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THIO-URACIL IN CHILDHOOD HYPERTHYROIDISM

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FROM the viewpoint of the pediatrician, hyperthyroidism in children has always been regarded as a primary medical problem. As a result, each new case is granted a thorough medical trial in the hopeful expectancy of an arrested disease process; inadequacy of these regimens is attested to by the proportion of hyperthyroid children who come to thyroidectomy. With the demonstrated effectiveness of thio-uracil, in controlling the symptoms of adult hyperthyroidism, pediatric management of the disease is worthy of further consideration.

Hyperthyroidism occurs infrequently in children. Bram,[10] in a series of 1,200 cases of thyroid disease in childhood, reported 0.8 per cent as hyperthyroidism. In a comparable study of exophthalmic goiter in all age groups, he reported 2.5 per cent as being in children. Somewhat more than 1.0 per cent of 15,500 cases at the Mayo Clinic occurred in children of 14 years or less. In a series of 13,200 cases of hyperthyroidism at the Crile Clinic, only forty-two cases were observed in children of this age group. Since 1922, at Children's hospital, twenty cases have had the considered diagnosis of hyperthyroidism.

The course of childhood hyperthyroidism may be benign or severe and acute. While the disease develops more rapidly in children than in adults, it is usually a relatively milder form. Reilly[9] indicates the tendency for multiple cycles of the disease, with succeeding cycles becoming less severe, but without total remission until full arrest occurs. It is these relatively benign cases with a tendency for self-remission which prove amenable to medical management. The development of hyperthyroidism in the adolescent child poses the additional problem and possibility of amelioration of thyrotoxic symptoms when the adolescent crisis is past. Because of the importance of the thyroid hormone in the normal development of the child, most investigators and all pediatric literature agree that each case warrants a thorough medical trial before surgery is considered.

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Medical treatment is preferably along conservative lines. In the initial stages of the disease, complete physical and mental rest are necessary, in so far as possible. Gradually increased patient contacts and interests are allowed, as governed by the clinical course of the patient. A general high-caloric, high-vitamin content diet is given, but all stimulants such as cocoa and the cola drinks are avoided. Discernible infectious foci are to be noted, with correction when the patient's condition permits. The importance of the thyroid gland as sequentially implicated in a constitutional neuroendocrine dysfunction is particularly stressed by Bram,[10] who advocates psychotherapy as a valuable adjunct in treatment. Understanding and cooperation of the patient's family forms the basis of this adjustment on the part of the patient.

In addition to these general measures, many and varied drugs have been used with the hope of symptomatic or specific relief. Of these, iodine is of proved value in a small percentage of cases. Phenobarbital and other barbiturates, quinine, insulin, and prostigmine all have had their advocates. Now, the use of thio-uracil, propyl thio-uracil, and radioactive iodine offers further possibility of medical management of the disease. It is to be emphasized that because of the tendency for spontaneous remissions of the disease process in children, the results of any form of therapy are necessarily guarded.

The writers have had the privilege of using thio-uracil in six cases of childhood hyperthyroidism. Case summaries to date follow:

CASE REPORTS

CASE 1.—B. R., a white girl aged 10, was admitted to Children's hospital Aug. 22, 1945, with a chief complaint of diarrhea that had not responded to treatment. The present illness dated to February, 1945, at which time a persistent diarrhea, accompanied by an elevated afternoon body temperature was present. Five to seven soft stools were passed daily, without accompanying digestive upset. In spite of vigorous symptomatic treatment, following cessation of therapy the disturbance recurred. For three months previous to admission, there had been weekly episodes of epistaxis. The mother stated that she had noticed a "rapid heartbeat' for about one year. There had been a weight loss of indeterminate amount, and the mother noted the child had become "thinner about the face." There were no complaints related to the neuromuscular system. Past medical history revealed only the usual childhood diseases. The maternal grandmother had "goiter," and symptoms of thyroid disturbance. Four siblings were living and well.

The patient was a thin, well-developed white female of the stated age, whose quickness of action drew immediate attention. The eyes were somewhat prominent, but there were no eye signs or exophthalmos present. The tonsils were enlarged and mildly reddened. The thyroid gland was palpably enlarged, without nodularity. The precordial rate was 90 to 120 beats per minute, and the precordial impulse was characterized as "strong and forceful." There were no murmurs. Examination of the lungs and abdomen was negative. Blood pressure was 110/50. There was a noticeable tremor of the extended hands, but the quadriceps test was not elicited. The patient weighed 24.1 kg. The child was placed on bed rest while laboratory procedures were pending.

On laboratory examination, catheterized urine specimens were sterile. Repeated stool examinations showed normal intestinal flora, and no evidence of parasitism. Blood agglutination tests for the typhoid-paratyphoid-dysentery organisms were negative. Blood counts were within normal limits, and the Kline test was negative. A tuberculin intradermal test with 0.01 mg. tuberculin was negative.

During the first week of hospital care, the patient had two or three formed stools daily, but a yellowish mucoid discharge exuded from the rectum almost constantly. This was of insufficient quantity to require the wearing of an absorbent pad. There was a low-grade afternoon fever present. On August 30, a blood cholesterol value was 245 mg. per cent. X-ray film of the wrists showed a bone age identical with the chronological age. A basal metabolic rate determination on August 30, was plus 26 per cent and plus 29 per cent. When no clinical improvement was noted following another ten days of inactivity, the patient was given thio-uracil in a dosage of 0.2 Gm. daily. At this time she weighed 24.5 kg. There was no immediate discernible change, although on September 11, the basal metabolic rate determination had fallen to plus 14 per cent. During the next month, however, she gained weight steadily to 28.6 kg.; her blood pressure averaged about 115/75, and she was less overly active. The frequency and consistency of the stools approached normal. The pulse remained extremely variable. On October 13, another basal metabolic rate determination was minus 9 per cent. Accordingly, she was discharged to the outpatient department on October 16, with instruction to take 0.1 Gm. of thio-uracil daily. She was asked to return at weekly intervals for progress examinations.

Inability to supply the medication necessitated a three-week interval when thio-uracil was not given. Because of this, she was asked to re-enter the hospital on Nov. 26, 1945. The parents stated that diarrhea was no longer a complaint, and that her behavior was more calm. They had noted a transient swelling in the thyroid area, although the gland seemed unchanged in size on examination. The pulse rate was 160 beats per minute, and the paper tremor of the extended hands was more evident. On November 27, basal metabolic rate determination was plus 28 per cent. The blood cholesterol was 221 mg. per cent. An electrocardiogram taken at this time showed only a sinus tachycardia of 150 beats per minute. On November 28, thio-uracil, in a dosage of 0.4 Gm. daily, was begun, together with phenobarbital in a dosage of 0.016 Gm. three times daily. Within one week the pulse rate steadied at 100 beats per minute. On December 13, another basal metabolic rate determination was plus 3 per cent. The patient was discharged the following day on a maintenance dosage of thio-uracil, 0.2 Gm. daily, and 0.032 Gm. of phenobarbital daily.

Bi-weekly clinic visits were continued. She gained weight slowly. The thyroid gland could no longer be palpated at the end of the third month. On March 26, 1946, a basal metabolic rate determination was minus 2 per cent, and the thio-uracil dosage was reduced to 0.1 Gm. daily. Her excellent health continued, and she was able to tolerate a return to school. On July 25, 1946 the basal metabolic rate determination was plus 8 per cent, and the thio-uracil dosage was reduced to 0.05 Gm. daily. At present the pulse rate averages 85 beats per minute. On November 9, the determination was minus 8 per cent. Thio-uracil was discontinued on this date. Blood pressure is 110/70. The child weighs 31.8 kg., and in all respects is developing and behaving normally. A minimal tremor of the extended hands and the need for monthly clinic check-ups are the only present evidence of her once active thyroid disturbance.

CASE 2.—J. P., a white female aged 14 years, was admitted to Children's hospital Sept. 17, 1945, because of an injury to the right elbow following a fall. She was the ward of a children's home where she had been considered a behavior problem because of emotional instability and "nervousness." She had always been thin-faced and was unable to gain weight normally. There were no gastrointestinal or cardiorespiratory symptoms, and menstruation was not established.

The maternal grandmother had required a thyroidectomy, and for reasons unknown, a tracheotomy had been performed two years later. Past medical history revealed a previous fracture of the same elbow in 1940, but was otherwise irrelevant.

On physical examination the child was apprehensive, and complained bitterly about any movement. She was well developed and fairly well nourished, weighing 48.6 kg. A diffuse enlargement of the thyroid gland was noted. There was no bruit. No exophthalmos or eye signs were present. There was a fine tremor of the extended left hand. There was a painful

swollen deformity at the right elbow, with marked limitation of motion. Cardiorespiratory and neuromuscular systems showed no abnormality.

Roentgenologic examination of the elbow showed a deformity due to previous fracture, and a recent fracture of the proximal end of the radius with angulation. Urinalysis was normal, the Kline test was negative, and the sedimentation rate and blood cholesterol values (203 mg. per cent) were within normal limits.

On September 18, under general anesthesia, an open reduction and excision of the radial head was carried out, and a cast was applied. The convalescence was uneventful, and on September 28, the cast was removed, and physical therapy initiated. During this period, frequent examinations by a series of examiners had directed the child's attention to her thyroid gland, and the unfortunate connotation of her grandmother's experiences was brought to mind. This in no way allayed her symptoms. Initial basal metabolic rate determination was made September 29, and two tests averaged at plus 25 per cent. Although the factors of the healing fracture and recent psychological disturbances were considered, a tentative diagnosis of hyperthyroidism was made, and thio-uracil in a dosage of 0.1 Gm. twice daily was begun.

She was continued on this dosage for two weeks, at which time the basal metabolic rate determination was unchanged; the dosage was then increased to 0.4 Gm. daily. During the subsequent two-week period, she gained 2 kg. weight, and was less emotional. A basal metabolic rate determination on November 1, 1945 showed a slight decrease to plus 23 per cent, and the child was discharged to the outpatient clinics on a maintenance dosage of 0.2 Gm. thio-uracil daily. Weekly white blood cell counts were taken. No immediate additional changes in the physical condition were apparent.

During the period following hospital discharge until May 15, 1946, she did not take thio-uracil with regularity, difficulties with her supervisor leading her to "even-up" by destroying the pills. On March 15, 1946, a basal metabolic rate determination was plus 37 per cent. At this time her symptomatology was much the same as on initial admission. In June, 1946, she again came under the care of her parent and was persuaded to follow a regular schedule. Accordingly, she was readmitted to Children's hospital to be regulated on another course of thio-uracil.

On this admission history of May 15, the mother noted that the patient had frequent "excitable fits" and "crying spells." The tremor of her hands was more marked, and the thyroid gland was unchanged in size. Her weight at this time was 51.0 kg., and the pulse rate averaged 110-120 beats per minute. A basal metabolic rate determination on May 16 was plus 37 per cent. Two white blood cell counts averaged 6,700 cells with about 39 per cent neutrophilic forms. She was given 0.4 Gm. thio-uracil daily. Blood counts were taken twice weekly during early regulation. On May 27 another determination was plus 27 per cent. At this time the patient weighed 52.7 kg., and her mannerisms and emotional behavior were uniform. Accordingly, she was discharged to her parents on a maintenance dosage of 0.2 Gm. thio-uracil daily. Arrangements were made for her family physician to take weekly blood counts, and she was asked to report any illness or untoward symptoms to him immediately.

She was seen in the outpatient clinic July 5, at which time she weighed 55.0 kg. Her pulse rate averaged 110, but no traces of jittery behavior existed. On August 8, she was hospitalized overnight for laboratory procedures. Basal metabolic rate determination averaged plus 8.5 per cent. The patient weighed 55.0 kg. at this time. Thio-uracil dosage was reduced to 0.1 Gm. daily for two weeks, and since, she has been maintained on 0.05 Gm. daily. She has continued in excellent health.

CASE 3.—C. B., a white girl aged 10 years, was initially seen in the outpatient department of Children's Hospital Feb. 20, 1946. The referring physician had made the tentative diagnosis of early chorea, chiefly on the basis of a "pounding heart." Questioning revealed that during the previous three weeks the patient had been "nervous" and cried easily without adequate cause. She also had "palpitations of the heart." When seen by her physician, she was advised to try absolute bed rest and phenobarbital sedation for two weeks. When,

during this time, she had no symptomatic improvement, she was sent to Children's hospital. She entered the hospital March 11, 1946. Previous to the onset of the presenting symptoms the child had been quiet and unemotional. There were no complaints referable to the gastrointestinal or neuromuscular systems. Family history and past medical history were noncontributory, although the mother admitted to "nervous exhaustion" several years previously. There was no familial history of thyroid disease.

Physical examination showed a well-developed and well-nourished child, who had atypical choreiform movements of the extremities. There was no exophthalmos. Tonsils were huge and cryptic. There was a diffuse enlargement of the thyroid gland; no bruit was audible. There was a soft systolic precordial murmur without thrill. A fine tremor of the extended hands was evident. Blood pressure was 120/50. Pulse rate was 90 to 110 per minute. Weight was 31.8 kg.

The patient was placed on absolute bed rest while diagnostic studies were pending. The sedimentation rate was 4-9-24 (normal 5-10-25), the Kline test was negative, and complete blood counts were within normal limits. An electrocardiogram taken March 11 was within normal limits, as was an orthodiagram of the same date. A chest x-ray film showed questionable enlargement of hilar glands on the right side. A tuberculin test with 0.01 mg. tuberculin was negative. The cardiology consultant, in evaluating the heart murmur, expressed the opinion that it was not due to an active carditis. The pulse rate varied from 90 to 129 beats per minute, and an afternoon fever of 99.5 to 100° F. was present. When, after two weeks of enforced inactivity and in the presence of an excellent appetite, the patient lost 1.5 kg. of weight, attention was redirected toward the thyroid gland. On March 26, a blood cholesterol determination was 165 mg. per cent. The basal metabolic rate determination on March 26 was plus 24 per cent and plus 21 per cent.

On March 27, phenobarbital in a dosage of 0.016 Gm. three times daily was started. No improvement was noted after one week, so on April 7 the patient was placed on thio-uracil in a dosage of 0.1 Gm. three times daily. During the following week the patient regained her entrance weight, but the hyperactivity was undiminished, and the pulse and body temperature curves were unchanged. A basal metabolic rate determination on April 21 was minus 3 per cent. On April 22, the thio-uracil dosage was reduced to a maintenance level of 0.1 Gm. daily, and she was discharged to the out-patient clinics, with instructions to return at biweekly intervals.

On the fourth return visit, May 6, the mother related that for ten days previously the child had limped on the left leg as evident on examination. There was a slight restriction of internal rotation at the left hip, and an area of tenderness over the inferior ramus of the left pubic bone. A tentative diagnosis of osteochondritis of this area was made, and the patient was hospitalized for observation. In addition to the localizing findings, the child still had a tremor of the extended hands and tongue, quick nervous movements, and a tachycardia with a forceful precordial impulse. A basal metabolic rate determination at this time was plus 17 per cent. Pelvic x-ray studies showed no bony abnormalities. The child was placed on complete bed rest, and thio-uracil dosage was increased to 0.2 Gm. daily.

On May 12, sudden pyrexia initiated the onset of acute follicular tonsillitis. The infectious process precipitated an agitated state similar to that seen on initial admission. Choreiform movements, constant lip-licking and protrusion of the tongue, and a throat culture that revealed numerous streptococcal forms again made chorea a strong possibility. Electrocardiographic studies were again normal, as was the sedimentation rate. Under penicillin therapy the throat findings resolved rapidly, and she was allowed full activity May 21, 1946. She was discharged from the orthopedic service to the outpatient clinics on June 6.

Another basal metabolism rate determination June 16 was plus 12 per cent. Thio-uracil was reduced to 0.15 Gm. daily. During this period she gained weight to 33.6 kg., and the mother felt that the child was more quiet than at any time since the onset of symptoms. On August 7, a basal metabolic rate was minus 7 per cent, and the thio-uracil was reduced to 0.05 Gm. daily. Since this time she has shown only a slight tremor of the extended hands, the goiter has regressed in size, and she has gained weight to 36.3 kg. The blood

pressure averages 95/65, and the pulse rate is 75 to 80 beats per minute. Thio-uracil medication was discontinued Sept. 20, 1946. Future program calls for early tonsillectomy and continued observation at monthly intervals.

CASE 4.—M. R., a white girl aged 13 years, was admitted to Children's hospital on April 2, 1946, with the chief complaint of "bulging eyes" of two weeks' duration. The mother had always felt that the child had a tendency to be nervous, but recently this had become more apparent, and the child had become emotionally labile. She had lost an unknown amount of weight, in spite of a voracious appetite. She was always tired and lacked the stamina of her siblings. There were no cardiorespiratory or gastrointestinal symptoms. Menstruation was not established.

Fig. 1.—Case 4. Appearance after four months' thio-uracil therapy.

The past medical history was noncontributory. Familial history of thyroid disturbance was present in the maternal grandmother, and one sister.

Physical examination showed a lanky, thin, but well-developed girl who darted quick glances about her. She responded to directions with overly rapid movements, and fidgeted on the examining table. There was a moderate degree of exophthalmos, and a definite lid-lag was present on looking down. No bruit was audible over the eyeballs or thyroid gland. The pulse rate was 100 per minute, and the blood pressure was 130/50. The thyroid gland was barely palpable, firm, and without nodularity. There was a fine tremor of the extended hands and protruded tongue. Examination of the cardiorespiratory and neuromuscular systems was essentially negative. The weight was 34.5 kg.

Laboratory studies revealed a blood cholesterol value of 194 mg. per cent, a negative Kline test, and a sedimentation rate of 3-9-20. After two days of bed rest, the basal metabolic rate determination was plus 25 per cent and plus 20 per cent on two readings.

Following admission to the hospital, and while studies were obtained, she was put on bed rest, and her activity was limited as much as possible. Thio-uracil in a dosage of 0.3 Gm. daily was begun on April 5. After one week's time the patient seemed better adjusted to hospital routine, and was able to rest more completely. The tremor of the hands became less obvious. On April 19, a basal metabolic rate determination was plus 15 per cent. The following day the dosage of thio-uracil was increased to 0.4 Gm. daily. At the end of the subsequent two weeks the pulse rate remained at a lower level, and the patient had gained weight to 39.9 kg. She was allowed gradually increasing activity at this time in preparation

for discharge. Another basal metabolic rate determination on May 1 showed a level of plus 8 per cent. She felt well, and was discharged to the outpatient clinics May 3 on a maintenance dosage of 0.2 Gm. thio-uracil daily.

The patient was followed in the laboratory at biweekly intervals, and examined at the end of two months. At this time the activity was perceptibly diminished, the exophthalamos was less, and the blood pressure was 120/75. When next seen on July 27, the basal metabolic rate determination was minus 2 per cent, and the patient weighed 42.3 kg. The thio-uracil dosage was reduced to 0.15 Gm. daily. When seen Sept. 14, the weight had increased to 44.1 kg. No signs of thyrotoxic activity were noted. Subsequently, thio-uracil dosage was decreased gradually to 0.05 Gm. on alternate days. On Nov. 2, 1946, the basal metabolic rate determination was plus 8 per cent. Thio-uracil was discontinued on this date.

On subsequent biweekly checkups, the patient has continued in good health. Observation will continue at monthly intervals.

Fig. 2.—Case 5. Appearance before treatment.

CASE 5.—M. S.,* a 9-year-old white girl, had a swelling of the neck for one month previous to admission to Children's hospital on June 26, 1946. This caused the child no discomfort, but had been noticeably enlarging. The neighbors had thought "her eyes were sticking out," and had mentioned this to the family. Because of this, the mother had consulted her physician. Questioning revealed that despite a ravenous appetite, the child had became steadily more thin, the amount of weight loss being unknown. For six weeks previously she had been very emotional and nervous. Although she had been regarded as "high-strung—we all are," this tendency was now pronounced. No symptoms referable to the gastrointestinal, cardiorespiratory, or neuromuscular systems could be ascertained. There was no familial history of thyroid disturbance. On June 24, a basal metabolic rate determination done at a private laboratory was plus 41 per cent. Hospitalization was advised.

Physical examination on June 26 revealed an alert, skinny child with marked bilateral exophthalmos. She was apprehensive, and jumped or was startled at any extraneous sound. Her hair was fine and silky. Exophthalmos was prominent, and lid-lag and "quick-look" were present. There was anterior fullness of the lower neck, and the thyroid gland was smoothly and symmetrically enlarged, roughly 4 × 5 cm. The pulse rate was 140 beats per minute. The blood pressure was 140/40. A functional systolic murmur was present at the apex, and bruits were audible over the eyeballs and thyroid gland. The skin was noted to be warm, the palms and soles being moist. There was a fine tremor of the extended hands. No quadriceps weakness was noted. The patient weighed 25.5 kg.

*Case of John Reynolds, M.D.

Urinalysis was normal, and the Kline test was negative. Blood cholesterol level was 162 mg. per cent. Wrist x-ray films for development of centers of ossification according to Todd, revealed the bone age to be slightly in excess of the chronological age. Two blood counts averaged 7,400 with 55 per cent neutrophilic forms.

On June 29, the patient was placed on thio-uracil, and was given 0.1 Gm. four times daily. At 4-day intervals, the white blood cell counts were 6,200, 5,500, and 4,400, with 38, 40, and 32 per cent neutrophilic forms, respectively. Accordingly, on July 8 the thio-uracil dosage was decreased to 0.2 Gm. daily. During this period the patient was allowed graduated activity from full bed rest to unlimited activity. She gained weight to 26.8 kg., the pulse rate was diminished to 110 beats per minute, the entrance symptom of jitteriness was lessened, and she was able to play quietly with other children. On July 9, 1946, a basal metabolic rate determination was plus 22 per cent. She felt well, and at the time of discharge, July 10, the white blood cell count was 6,500, with 35 per cent neutrophilic forms.

She was followed as an outpatient at biweekly intervals, and the blood counts remained at this level. On July 21, the thio-uracil dosage was reduced to 0.15 Gm. daily. She gained weight steadily to 27.7 kg., and the mother felt the eyes were less prominent. Her sleep was undisturbed, her appetite was excellent, and general health remained good. On August 14, the pulse averaged 100 beats per minute; the blood pressure was 130/75. The size of the thyroid gland was unchanged. The precordial murmur had disappeared, as had the bruits previously audible over the eyeballs and thyroid gland. Accordingly, the dosage of thio-uracil was reduced to 0.1 Gm. daily. On August 28, the white blood cell count was 6,500, and the neutrophilic forms had fallen to 24 per cent. With the reduction of thio-uracil to 0.05 Gm. daily, the count on Sept. 25, 1946 was 8,000, with 46 per cent neutrophiles. Some return of thyrotoxic symptoms has recurred with this dosage, and increased dosage required for control of these symptoms has produced neutropenic tendencies. Therefore, she has been shifted to a corresponding dosage of propyl thio-uracil, and clinical and laboratory observation is continuing.

CASE 6.—P. K., a white girl aged 7 years, has been under the pediatric supervision of one of us (F. R. J.) since infancy. When seen in March, 1944, she had evidence of an acute upper respiratory infection. There was a moderate pharyngitis and cervical adenitis. Symptomatic treatment was given. A low-grade fever present at this time persisted after all other evidence of acute infection had disappeared. Sedimentation rates and complete blood counts at this time were within normal limits.

In June, 1944, she was again seen because of a persistence of this low-grade fever, and an additional complaint of "palpitations of the heart." The pulse rate ranged from 100 to 130 beats per minute, and had been noted to be increasingly rapid. Her eyes were noticeably prominent without true exophthalmos. There was a tremor of the extended hands. a soft systolic murmur was audible over the precordium, and the heart action was tumultuous, A definite thyroid enlargement was noted. Accordingly, a diagnosis of hyperthyroidism was entertained.

The patient was placed on bed rest at home, and was given 10 drops of Lugol's solution daily. A basal metabolic rate determination after two weeks of iodine therapy was plus 29 per cent. The thyroid gland was noticeably increased in size. On August 30, a basal metabolic rate determination was plus 26 per cent, and the blood cholesterol determination was 132 mg. per cent. Bed rest and iodine medication were continued. On Sept. 19, 1944, another basal metabolic rate determination was plus 21 per cent. On the following day, thio-uracil in a dosage of 0.1 Gm. three times daily was started. This dosage was decreased after two weeks to 0.2 Gm. daily, and further decreased after another two weeks to 0.1 Gm. daily. This dosage was continued for one month. On Oct. 17, 1944, a basal metabolic rate determination was plus 11 per cent, and the blood cholesterol determination was 185 mg. per cent. The pulse rate at this time averaged 95 beats per minute, and the complaint of palpitations was no longer present. The thio-uracil dosage was decreased to 0.05 Gm. daily, and remained so for four months, when it was discontinued. On November 28, the basal metabolic rate determination was plus 15 per cent; on Jan. 23, 1945, it was plus 11 per cent.

The systolic murmur was no longer audible, and the patient was allowed increased activity. On May 1, 1945, the basal metabolic rate determination was plus 12 per cent; on July 30, it was plus 13 per cent. It is to be emphasized that during this period the child carried on a fairly normal life with restrictions only from extremes.

On Dec. 15, 1945, the basal metabolic rate determination had risen to plus 20 per cent and although all physical and subjective evidences of thyrotoxicosis had disappeared, thio-uracil in a dosage of 0.15 Gm. daily was begun. On March 16, 1946, with the dosage of thio-uracil reduced to 0.05 Gm. on alternate days, the basal metabolic rate determination was plus 22 per cent. On June 22, after completion of two weeks of day camp activities entailing considerable excitement, it had risen to plus 38 per cent. The mother insisted the child had no aggravation of symptoms, and had remained quite calm. For the following week the thio-uracil dosage was again increased to 0.15 Gm. daily, and was then reduced to 0.05 Gm. daily. On August 14, the basal metabolic rate determination was plus 13 per cent.

At present, thio-uracil medication has been discontinued and the child allowed fairly normal activity. She is enjoying unrestricted school activities, and none of the original subjective or objective findings are evident. Observation at intervals will continue.

COMMENT

In this brief series, no notable reactions to the administration of thio-uracil have been observed. In Case 5, a moderate leucopenia could be controlled by reduction of drug dosage. It is felt that this case, unless shown to do well with propyl thio-uracil, will require thyroidectomy. Every case showed an eosinophilic blood reaction, reaching its peak about the sixth week of thio-uracil therapy, averaging about 15 per cent of the differential count. This proportion diminished slowly, but a relative eosinophilic increase persisted as long as thio-uracil therapy was continued. This is regarded as individual sensitization to thio-uracil.

There is no hard and fast rule by which termination of treatment can be predicted. Williams[13] concluded that except in a few cases in which there are toxic reactions to thio-uracil, the drug can be used indefinitely, and that as long as it is used, a remission of the disease is maintained. The recent excellent summarization of Beierwaltes and Sturgis[3] offers the opinion that thio-uracil therapy may be discontinued at the end of an average of ten months with the prospect that 60 to 80 per cent of patients will experience a relatively persistent remission of symptoms. Burke[5] reported a case in a female aged 10, in which drug-induced remission had persisted one year following twelve months of thio-uracil therapy. Bram,[10] in discussing medical treatment of childhood hyperthyroidism, believed that two consecutive normal basal metabolic rate determinations indicated at least temporary remission of thyroid overactivity. It is our practice to decrease or increase amounts of the drug given each patient on the basis of present requirements and previous response. Following this criterion, the patient in Case 1 has received the drug continuously for thirteen months, while the one in Case 3 was under thio-uracil therapy for but five months.

We are unable to evaluate these cases as to permanency of cure, since the period of observation has been too brief. However, these children while under treatment with thio-uracil and with restrictions from the extremes of physical and mental activity, have carried on reasonably normal lives. Exacerbation of symptoms while under stress has been readily controlled by treatment gauged to their

apparent needs. In the case of adolescent patients, it is felt that thio-uracil therapy might well cause the symptoms of hyperthyroidism to remain in remission until controlled by the establishment of the more stable period of adulthood. Though subtotal thyroidectomy may be required at one time, we feel that an advantage has been gained by retaining thyroid action at the time of the individual's greatest need, for future needs.

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INFECTIOUS HEPATITIS IN CHILDHOOD

A Report of Two Institutional Outbreaks and a Comparison of the Disease in Adults and Children

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INFECTIOUS hepatitis (which is now believed to be the same disease as catarrhal jaundice) has long been recognized as occurring sporadically and in epidemic form in both civilian and military populations. During wartime it has been prevalent among troops, particularly in places where living quarters were crowded and sanitary conditions poor. In contrast, during peacetime it is said to be primarily a disease of childhood,[1-4] appearing either sporadically or in epidemics in schools, camps, and institutions. Family outbreaks involving several children are not uncommon. Blumer,[2] in reviewing fifty epidemics occurring before 1923, found that about 70 per cent of these involved the younger age group. In several outbreaks reported subsequently, 65 to 100 per cent of cases have occurred in children.[3-10] Because of certain inherent difficulties in investigating this disease, and also possibly because of its usually mild and apparently benign course in childhood, little attention was directed toward the juvenile type. But with the appearance of the more severe adult forms in soldiers, the military importance of infectious hepatitis became evident, and efforts were applied toward the elucidation of some of its fundamental problems. Recent investigations have resulted in certain new information on the etiologic agent,[11] its possible manner of spread,[12, 13] and its prevention.[14-16] Thus it has been shown in experiments employing human volunteers that the etiologic agent is filtrable and resistant to a temperature of 56° C. for thirty minutes. It is believed to be a virus. This agent is known to be present in the feces and blood of patients in the acute phase of disease, and there is experimental evidence that the intestinal-oral route may be of importance in its spread, since the disease may be produced in human volunteers by feeding infective feces.[17-20]

There is no reason to believe that infectious hepatitis, which has appeared in large outbreaks among troops during World War II, differs from catarrhal jaundice which appears sporadically or in outbreaks among children. Experimentally there is some support for this concept furnished by immunologic evidence which shows that adult human volunteers, convalescent from hepatitis induced by the administration of a strain of virus obtained from the feces of children with the disease in the United States, were immune when reinoculated with a strain of virus derived from the stool of a soldier in the acute phase of epidemic infectious hepatitis contracted in Sicily.* Both strains of virus used in this

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*Personal communication to W. P. H. from J. Stokes.

experiment also produced homologous immunity. Nevertheless, complete proof of the identity of the two diseases is lacking. This is due in part to lack of a satisfactory serologic test and susceptible laboratory animals. Experiments using human volunteers have been necessarily limited in number and therefore of limited statistical value. It has not been possible as yet to explore the occurrence of various strains of virus which may have distinct serologic characteristics. Until such investigations have been made, the identity of different outbreaks of infectious hepatitis caused by various strains of virus cannot be established.

As a result of the war experience with infectious hepatitis among troops, considerable data concerning clinical manifestations in adults have been accumulated[21-25] and it is evident that there are certain differences between the characteristics of the disease as it appears in adults and children. These differences are related principally to severity of the infection; inasmuch as they have thus far received little emphasis, it is the object of this paper to describe two epidemics of infectious hepatitis in children and to compare the clinical course of disease in children with that reported in adults.

CLINICAL MATERIAL AND METHODS

Two institutional outbreaks of infectious hepatitis were studied. In one, fifty-three cases of hepatitis with jaundice occurred, along with fifty-six cases of questionable hepatitis without icterus.* A description of this epidemic and the use of gamma globulin as a prophylactic measure in the exposed population has appeared elsewhere.[15] In the other institution, sixty-eight patients developed hepatitis with jaundice; of these, forty-four (65 per cent) were children. In this report only those cases with jaundice and in the age group under 16 years will be considered. Since the two epidemics involved children of different types who are not comparable, the outbreaks will be described separately.

Highland Heights.—In November, 1944, infectious hepatitis appeared in a Catholic home for children in New Haven. The home is situated just beyond the central part of the city, and consists of one large building housing approximately 300 children and thirty-nine adults. At the time of the epidemic, 90 per cent of the children were between the ages of 6 and 16 years. During the period of November, 1944, to March, 1945, there were fifty-two cases of infectious hepatitis with jaundice among the 300 children, and a single case among the thirty-nine adults. In forty-four (84.6 per cent) children the clinical course could be divided into two phases: (a) a preicteric phase, from the onset of symptoms to the appearance of jaundice; and (b) an icteric phase, lasting until clinical jaundice disappeared. Eight children (15.4 per cent) had asymptomatic jaundice as the presenting complaint. In the typical case, the preicteric phase began abruptly with headache, fever, and gastrointestinal symptoms. Of the last, abdominal pain and vomiting were the most prominent, with anorexia and nausea occurring less frequently. In Table I are recorded the most commonly occurring symptoms in the preicteric phase in the Highland Heights children, with comparable tabulations for two groups of adults with infectious hepatitis.

*Acknowledgment is made to Dr. Paul L. Boisvert for calling our attention to this outbreak, to Sister Mary Catherine Teresa and members of the staff at the St. Francis Orphan Asylum, and to Dr. Joseph D'Amico of New Haven, Conn., for their cooperation.

TABLE I. RELATIVE FREQUENCY OF PREICTERIC PHASE SYMPTOMS

SYMPTOMS	CHILDREN: 44 INSTITUTIONAL CASES* NO.	%	ADULTS: 167 MILITARY CASES† NO.	%	27 EXPERIMENTAL CASES‡ NO.	%
Anorexia	10	22	138	82	26	96
Nausea	10	22	126	75	16	59
Vomiting	23	52	55	33	6	22
Fever	24	54	90	53	27	100
Abdominal Pain	25	56	73	42	21	77
Headache	33	75	59	35	20	74

*These are children in the Highland Heights outbreak.

†Figures taken from a clinical description of infectious hepatitis in American troops.[21]

‡These cases occurred in volunteers who were among those who served as subjects for the transmission of infectious hepatitis in experiments conducted by the Neurotropic Virus Disease Commission, United States Army.[23, 32, 34] The series is small but the experimental cases were studied with special care.

TABLE II. DURATION OF PREICTERIC AND ICTERIC PHASE AND FEVER IN THREE GROUPS OF PATIENTS WITH INFECTIOUS HEPATITIS

	PREICTERIC PHASE: NO.	DURATION (DAYS)	AVERAGE NO. DAYS	ICTERIC PHASE: NO.	DURATION (DAYS)	AVERAGE NO. DAYS	FEVER: NO.	DURATION (DAYS)	AVERAGE NO. DAYS
Children*	58	1-15	4.8	96	2-32	9.8	48	1-10	3.8
Military cases†	167	1-18	5	200	4-83	27	90	2-15	5.0
Experimental cases†	27	3-21	7-2	27	8-31	20	27	4-14	7.9

*Institutional cases in the Highland Heights and Southbury outbreaks.

†Same legends as Table I.

Among the children, diarrhea and constipation were rare, as were malaise, chills, and generalized aches and pains. Usual temperatures ranged from 99.6 to 101° or 102° F. but occasionally to as high as 105° F. (rectal), the highest temperature usually being at the onset of disease and declining during the ensuing four to five days of the preicteric phase to normal. The preicteric period averaged about five days, after which jaundice became evident. With the appearance of jaundice, a striking amelioration of symptoms occurred. The temperature remained normal, the gastrointestinal disturbances vanished, appetite was excellent, and the child felt quite well almost at once. All of the children were hospitalized in the institution infirmary until clinical jaundice disappeared. The duration of jaundice in the fifty-two children ranged from two to thirty-two days, averaging eleven days (Table II). There were no seriously ill patients in this outbreak. Complications were infrequent, consisting of atypical pneumonia in one child and generalized acute dermatitis in two children. One relapse occurred in a child two and one-half weeks after his discharge from the infirmary. The one adult who contracted the disease in this outbreak had a similar but more severe course than the average juvenile patient, with deeper and more prolonged jaundice and gastrointestinal symptoms.

Southbury Training School.—The second outbreak occurred at the Southbury Training School for the Feeble Minded, located in a rural setting near Southbury, Conn.* This institution has an average patient population of 1,300,

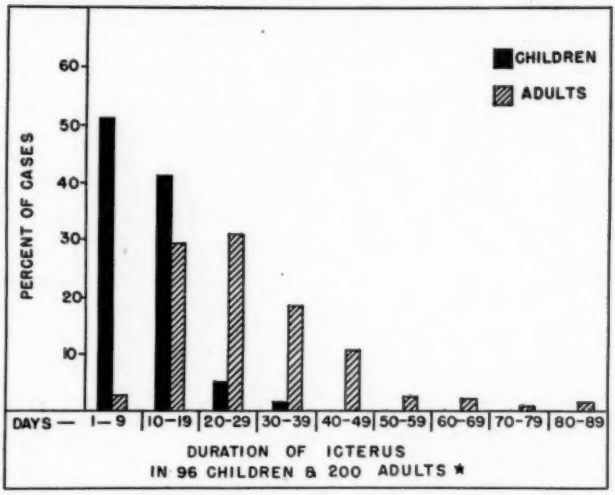
*Acknowledgment is made to Dr. Herman Yannet, medical director of the Southbury Training School, for his assistance and cooperation.

consisting of low, middle, and high-grade mental defectives housed in groups of twenty to eighty in separate cottages according to mental and chronological age. The chronological ages range between 5 and 65 years with the majority between 6 and 16 years.

In July, 1945, two cases of infectious hepatitis developed in a cottage for infirm patients, and during the next four months there were six cases scattered in several cottages. By the end of November, there was a sudden increase in cases in two adjacent cottages housing low-grade mentally defective boys, most of whom were bed ridden and incontinent of urine and feces. Forty of the one hundred sixty-seven patients in these two cottages developed infectious hepatitis with jaundice in the subsequent two months. At the same time, sixteen cases appeared among the remaining cottages. In all, sixty-eight cases of hepatitis with jaundice developed between July 10, 1945, and March 4, 1946. Forty-four (65 per cent) of these occurred in the age group under 16 years; eighteen (27 per cent) were between 16 and 25 years; and six (8 per cent) were 26 and over. The symptoms of the forty-four children to be described here differed from that of the Highland Heights patients, but the difference is probably more apparent than real. Since the Southbury group represents low-grade mental defectives for the most part, subjective symptoms could not possibly be elicited from the majority of patients, and only fourteen (32 per cent) are recorded, therefore, as having a preicteric phase, while in thirty (68 per cent) jaundice was the presenting symptom. In nine of the fourteen patients (64 per cent) who were known to be sick before the appearance of jaundice, fever and vomiting were the consistent abnormalities. In only three patients were subjective symptoms recorded: one complained of nausea, and two of headache. The fevers ranged from 100° to 105° (rectal), and, as with the group described previously, declined toward normal over a period of five days as the jaundice appeared. In a few patients, fever and vomiting persisted through the first day or two of jaundice. In forty-one (93 per cent), however, the icteric phase was completely asymptomatic. Jaundice was mild and persisted for an average of eight days with a range of three to twenty-one days. In only two patients were the elicited symptoms and signs suggestive of nonicteric hepatitis. Thirty-two patients were hospitalized, the length of hospital stay varying between one and twenty days, and averaging seven days.

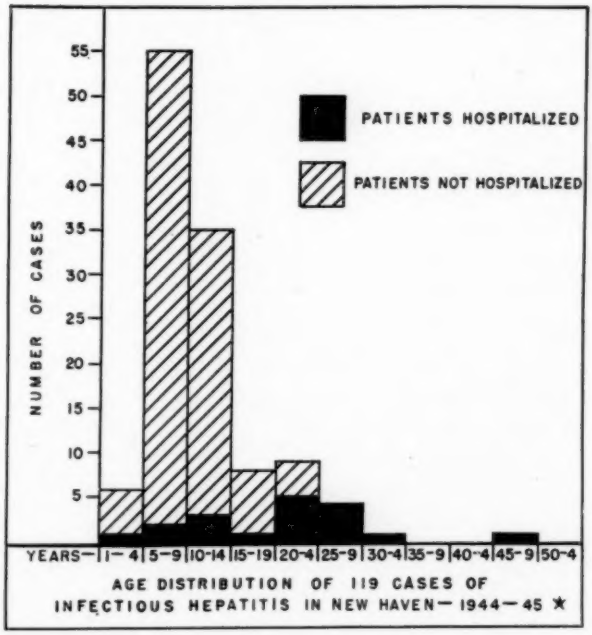
Laboratory work on the hospitalized group included the determination of the total number of leucocytes as well as examination of stained smears of the peripheral blood, examination of the urine for increase in bilirubin and urobilinogen, and determination of serum icterus index. Ordinarily the leucocyte count and icterus index were performed on admission to the institution hospital, so that only normal figures are recorded for a certain number of patients who subsequently developed obvious jaundice. Twelve patients had leucopenia, with less than 5,000 leucocytes per cubic millimeter; eighteen patients had between 5,000 and 10,000 leucocytes per cubic millimeter; only six patients had more than 10,000 white blood cells per cubic millimeter. Polymorphonuclear leucocytes numbered as few as 450 cells and lymphocytes as few as 400 cells per cubic millimeter during the period of leucopenia in certain patients in the

CHART 1.



★ Adult Cases Taken from Havens, W.P. —J.A.M.A. — 126, 17-23, 1944

CHART 2.



★ HIGHLAND HEIGHTS CASES NOT INCLUDED

preicteric phase. Numerous atypical lymphocytes such as have been described in infectious hepatitis[26-29] appeared in the peripheral blood during the acute phase of the disease.

DISCUSSION

In this paper, attention has been directed to the concept that infectious hepatitis as it occurs in epidemic form among troops and catarrhal jaundice as it appears among children, are probably the same disease but differences in severity of clinical manifestations are evident (Chart 1). That the adult and childhood diseases are probably identical is suggested by the fact that in all civilian outbreaks in which adults and children are exposed, a certain number of cases occur in individuals over the age of 16 years. In New Haven, during the winter of 1944-1945, when the Highland Heights institutional outbreak occurred, 119 additional cases were reported in the city.* Of these, only nineteen (16 per cent) were in individuals over 16 years of age. Chart 2 illustrates the age distribution of these cases, and calls attention to the fact that of the nineteen patients whose disease was serious enough to require hospitalization, thirteen (69 per cent) were in the adult group. Thus as in other civiliain outbreaks, a certain number of cases occurred in adults, and the adults seemed to have a more severe disease.

The striking feature of the two outbreaks of infectious hepatitis among children described here was the mildness of symptoms and their short duration. Characteristically, by the time jaundice appeared these children felt well and it was difficult to keep them in bed. In contrast is the persistence of anorexia, nausea, abdominal discomfort, and often vomiting for eight to ten days in the adult case of average severity. These facts are in agreement with the findings of others.[10, 30, 31] Among the ninety-six children described here there were no examples of severe hepatitis with prolonged jaundice or protracted convalescence as have been reported frequently in adults and occasionally in children.[1, 32] In Chart 1 is compared the duration of icterus in the ninety-six children and 200 adults who represent military cases with infectious hepatitis in the Middle East. The majority of children in this series fall in the "mild disease" group. The highest icterus index reported for the Southbury group was forty-seven units, and in only six (6.3 per cent) of the total ninety-six patients comprising both groups of children did jaundice persist for more than nineteen days. There were no deaths from infectious hepatitis in the juvenile group.

Although it is possible that differences in severity of infectious hepatitis could be due to variations in virus strains, the observations reported here bear out what has been noted previously. Cockayne[1] in an early review of the disease pointed out that children, who are so prone to exhibit vomiting and diarrhea with any gastrointestinal disturbance, frequently have less marked symptoms of this kind with catarrhal jaundice than do adults. Cullinan[31] and Ford[10] have also noted the tendency for the disease to be more severe in adults than in children. In the one adult case in the Highland Heights outbreak and in the patients over 16 years of age in the Southbury group of cases, the icteric indices tended to be

*We are indebted to Dr. Joseph I. Linde, Health Officer of New Haven, for the collection of data on cases occurring in the city.

higher and the duration of jaundice longer than in the children affected. However, although there were no severe cases among the children studied in these two outbreaks such cases do occur, and examples of prolonged jaundice with relapses and even death have been reported in children.[1, 32]

The difference between the severity of infectious hepatitis in children and in adults is comparable to the difference which exists between the childhood and adult forms of the more common virus infections. Measles, mumps, and chicken pox are all likely to be more severe and attended by more severe complications in the adult than in the child.

SUMMARY

Two institutional outbreaks of infectious hepatitis among children were studied. In all of the ninety-six junvenile patients the disease was mild and of relatively short duration as compared with statistics on the adult disease.

The mildness of infectious hepatitis in children has tended to belittle the disease. There is no evidence that such mild cases are less dangerous to the community from the infectious standpoint than are the more severe adult cases.

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HYPERCALCEMIA AND IDIOPATHIC HYPERPLASIA OF THE PARATHYROID GLANDS IN AN INFANT

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THE presence of extreme hypercalcemia in a patient who had hyperplasia of the chief cells of all four parathyroid glands is difficult to reconcile with the prevailing views on the abnormalities of serum calcium concentration in relation to the pathology of the parathyroid glands.[1] Chief cell hyperplasia has been associated with secondary hyperparathyroidism, and although instances of hypercalcemia have been reported as resulting from secondary hyperparathyroidism, it is difficult to conceive of such a disturbance on present theoretical grounds. Indeed, as pointed out by Albright,[2] the cases used to exemplify this contention were incompletely studied. Primary hyperparathyroidism associated with enlargement of all four parathyroid glands has been generally conceded to have distinctive histologic alterations in glands. Large cells of the water-clear type alone comprise the parathyroids in all the accepted cases reported to date.[1, 3]

Explanation of the underlying disturbance in this case of a 10-month-old infant with extreme hypercalcemia and enlargement of all four parathyroid glands might contribute much to the knowledge of disorders of calcium and phosphorus metabolism. It is hoped that the description of this patient will lead to the discovery of similar patients and subsequent clarification of the nature of the disorder.

CASE REPORT

The patient was a white male infant who was studied in the Infants' Hospital from the fifteenth to the twenty-fifth weeks of life and again from the thirty-seventh to the forty-third weeks. Hypercalcemia was revealed during the first admission and most of the subsequent investigations were designed to discover the cause of this abnormality.

The patient's family history disclosed no relevant disturbances. One 7-year-old sibling was said to be healthy. The pregnancy and delivery were normal. The birth weight was 7 pounds and was not regained until the thirteenth day, although both breast and complemental feedings were given during this period. The only disturbance during the neonatal period was icterus without anemia during the first week. From the second to the fifteenth weeks of life an adequate milk modification formula supplemented by 5 drops of oleum percomorphum was offered. Thereafter a variety of modified formulas were tried and solid foods were introduced at five months, although they were always taken poorly. A diet low in calcium (160 to 210 mg. per day) was given during the last week of life. The supplements of vitamin D are recorded in Table I.

From the first few weeks of life until the forty-second week, the patient's symptoms, both from the history and observations in the hospital, consisted of weakness, hypotonia, lethargy, poor appetite resulting in the refusal of much of the food offered, persistent constipation, and occasional episodes of forceful vomiting. Isolated rises of temperature up

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TABLE I. VITAMIN D INTAKE

AGE (WEEKS)	VITAMIN D (U.S.P. UNITS PER DAY)
3-5	720
6-14	900
15-17	1,500
18-20	1,000
21-22	3,000
23-24	0
25-37	800
38-	0

to 102° F. were recorded approximately once a week during both periods of hospitalization, although persistent fever was uncommon. Apparent tenderness of the extremities was noted when the patient was 8 months old.

Physical examinations consistently revealed a small, poorly nourished, weak, irritable child appearing chronically ill and apparently retarded in physical activity and mental capacity. In addition, a firm, smooth liver edge was palpable 2 cm. below the costal margin, and firm masses were felt in the region of each kidney. These latter masses were interpreted as representing slight enlargement of each kidney. Body measurements were consistently below the ten percentiles for normal individuals in the same age group. The patient weighed 8 pounds 7 ounces at 15 weeks of age; 10 pounds 2 ounces at 25 weeks and 11 pounds 8 ounces at 41 weeks. The course of the patient was essentially unchanged until the final week of life. The treatment during the two hospital admissions is outlined as follows:

During the first hospital admission, the patient received elixir of ferrous sulphate for nine weeks; sulfadiazine plus potassium citrate for eight weeks; penicillin, 40,000 units per day, during the fourth to sixth weeks in the hospital; two transfusions of citrated whole blood during the fifth week; and daily intramuscular injections of crude liver extract or vitamin B complex during the last six weeks.

During the second hospital admission, the patient received 40,000 units of penicillin daily until five days before death. A transfusion of citrated whole blood was given three weeks after admission, and elixir of ferrous sulphate was begun at that time. One gram of sodium bicarbonate was given daily during the last sixteen days of life. A specimen of the tibia was taken for biopsy during the second admission.

In the last week of life the patient began to vomit frequently. Two days before death the temperature suddenly rose to 104° F. Physical examination at that time revealed a seriously ill infant with mild cyanosis, labored respirations accompanied by retractions of the supraclavicular and subcostal soft parts, and dullness over the left lung. Coarse rhonchi were present throughout both lung fields. The extremities were cold and mottled. Fluoroscopic examination of the chest showed increased bronchovascular markings bilaterally and slightly increased density throughout the left upper lobe. Treatment with penicillin, oxygen, and fluids did not lower the patient's temperature, although there was slight clinical improvement. During the second day of this episode the patient died, apparently of respiratory failure.

Laboratory Measurements.—Table II summarizes the measurements of serum calcium, phosphorus, phosphatase, sodium, chloride, proteins, nonprotein nitrogen, and pH.

The red blood cell counts ranged from 3 to 4 million per cubic millimeter. The white blood cell counts ranged from 8,000 to 16,000 averaging about 12,000 per cubic millimeter.

Repeated examinations of the urine revealed irregular fluctuations in albumin from 0 to 1+, occasional green reduction of qualitative Benedict's solution, and normal urinary sediments. During the interval from 22 to 41 weeks of age, the urine was tested ten times with Sulkowitch's reagent. Little or no calcium was visibly precipitated seven times, although there were, interspersed among these negative reactions, three 2+ reactions. Several measurements of the amounts of calcium and phosphorus excreted in the urine per twenty-four hours are recorded in Table III.

TABLE II. SERUM MEASUREMENTS

AGE (WEEKS)	SERUM CALCIUM (MG. %)	SERUM PHOSPHORUS (MG. %)	SERUM PHOSPHATASE (BODANSKY UNITS)	SERUM PROTEIN (GM. %)	SERUM SODIUM MEQ. PER L.	SERUM CHLORIDE MEQ. PER L.	SERUM HCO_3 MEQ. PER L.	SERUM PH	NON-PROTEIN NITROGEN (MG. %)
21	19.	3.7	12.9	6.0			20.4	7.40	38.4
22	16.9			6.91	137	125			
24	14.8	4.35	12.5	5.8	133	114	18.9	7.30	
27	12.6	2.95	11.0	6.1		111			
37	14.9	3.3	10.3	6.7		106	18.5		30.5
40	19.5			A = 4.69 G = 2.47	137	106	23.		
41						101	22.	7.46	29.5
42	22.1			A = 5.27					
43*	17.3	7.8	8.5	G = 2.28		136			93.

A = Albumin.
G = Globulin.
*Blood taken just prior to death.

TABLE III. MEASUREMENTS ON TWENTY-FOUR HOUR SPECIMENS OF URINE

VOLUME* (C.C.)	SPECIFIC GRAVITY	PH	CALCIUM* (MG.)	PHOSPHORUS* (MG.)	TOTAL NITROGEN* (MG.)	PROTEIN* (GM.)	AMMONIA* (MG. N)	AGE (WEEKS)
439			16.4	384	3117	0		23
302	1.023	5.8	20.	310	2416			38
266	1.023	5.4	8.5	304	2394		115	38
290	1.016	6.0	31.4	226			106	42

*Amounts per twenty-four hours.

The concentration of trypsin in the duodenal contents was normal.

The total serum bilirubin was 0.1 mg. per hundred cubic centimeters. The subcutaneous injection of 0.13 c.c. of 1:1,000 solution of epinephrine hydrochloride provoked a slow rise in the nonfasting blood sugar level from 103 to 123 mg. per hundred cubic centimeters in sixty minutes. A measurement of the urea clearance was performed shortly after the patient was admitted for the second time. The blood cleared of urea per minute was 39.5 c.c., which is approximately 53 per cent of the normal value. During the forty-second week of life, simultaneous measurements of the concentration of calcium in the serum and cerebrospinal fluid revealed values of 22.1 and 8.0 mg. per hundred cubic centimeters respectively. The serum potassium measured in the last sample of blood drawn was 5.8 milliequivalents per liter. A single, three-day metabolic period to determine the balances of calcium, phosphorus, and nitrogen was accomplished during the twenty-fourth week of life. The results are depicted in Table IV. Due to the severe degree of constipation it cannot be assumed that the stools ascribed to this period represented the total fecal output derived from the measured intake.

TABLE IV. THREE-DAY BALANCE PERIOD* (AGE, 23 WEEKS)

	CALCIUM (MG.)	PHOSPHORUS (MG.)	NITROGEN (GM.)
Intake	1,025	758	4.33
Urine	16	384	3.12
Stool	806	184	0.37
Balance	+203	+190	+0.84

*Amounts per twenty-four hours.

During the thirty-eighth week of life an electroencephalogram revealed a normal tracing, consisting principally of 4 to 6 waves of normal amplitude per second. At about the same time an electrocardiogram was taken. There was sinoauricular tachycardia with a rate of 140 per minute. The P-R interval was 0.14 second and the Q-T interval was 0.23 second, which is shorter than the average of 0.26 second.[4] The electrical axis deviated slightly to the right. There was a one millimeter elevation of the S-T segment in Lead I.

Roentgenographic Examination.—Multiple roentgen examinations of the chest, long bones and skull were made during the patient's admissions to the hospital. On serial examination the changes were found to be essentially similar to those seen on the initial films.

Examination of the chest revealed no definite abnormality of the heart; the lungs showed considerable irregularity of aeration with peripheral emphysema and multiple small and poorly visualized areas of focal atelectasis. Throughout each lung the interstitial markings were increased in prominence and there were a few scattered areas suggestive of peribronchial inflammatory reaction. The changes were interpreted as being consistent with a diffuse interstitial pneumonitis with emphysema and lobular atelectasis.

The bones of the thorax, the skull, and the long bones were slightly undercalcified. The trabeculae of the spongeosa seemed diminished in number but increased in prominence. The cortex, particularly of the long bones, showed slight irregularity with some loss of cortical substances at the diaphyseal extremities. The zones of provisional calcification appeared well preserved and there was no definite evidence of uncalcified osteoid tissue to suggest rickets.

Roentgen examination of the abdomen and intravenous urograms showed slight enlargement of the liver and each kidney. Diodrast appeared promptly in each renal pelvis in five minutes and was transported normally to the bladder. There was no evidence of obstructive uropathy or other abnormality except for the slight enlargement of the kidneys. Calcification of the soft tissues could not be detected.

Biopsy.—A biopsy of the tibia, taken seventeen days before death, revealed fibrosis of the marrow spaces, a disturbance of bone growth, and hyperplasia of the remaining hematopoietic elements. On the basis of these findings, a diagnosis of hyperparathyroidism was suggested.

AUTOPSY

Postmortem examination was performed four hours after death and was limited to examination of the abdominal and thoracic contents. The body was that of a poorly developed and poorly nourished infant, measuring 63 cm. in length (normal length, 69 cm.).[5] Examination of the external surface of the body revealed a 4 cm. healed, vertical incision on the anterior surface of the middle third of the tibia.

The weights and measurements of the viscera, with normal weights in parentheses,[5] were: heart, 36 Gm. (39 Gm.); lungs, 80 Gm. (105 Gm.); spleen, 5.6 × 3.5 × 1.2 cm., 13 Gm. (22 Gm.); thymus, 4.7 × 4.7 × 1.3 cm., 8 Gm. (20 Gm.); liver, 16.5 × 8.2 × 4.5 cm., 218 Gm. (274 Gm.); right kidney, 6.7 × 3.8 × 2.3 cm., 40 Gm. (32 Gm.); left kidney, 7.2 × 3.5 × 2.5 cm., 38 Gm. (31 Gm.); right adrenal, 3.7 × 2.3 × 0.5 cm., 2 Gm.; left adrenal, 3.9 × 1.7 × 0.3 cm., 2 Gm.; testes, 1 Gm. each; and parathyroids, 0.8 × 0.2 × 0.2 cm., 0.5 × 0.2 × 0.1 cm., 1.0 × 0.4 × 0.2 cm., and 0.6 × 0.3 × 0.2 cm.

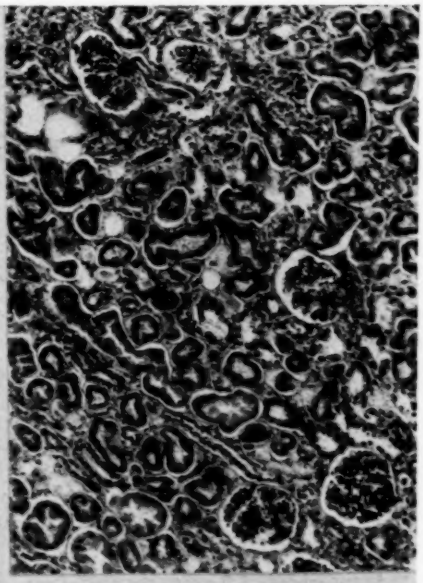
The pericardial, pleural, and peritoneal cavities were lined by smooth, moist, and glistening membranes. Two cubic centimeters of clear fluid were present in the pericardial sac, but no free fluid was found in the pleural or peritoneal cavities.

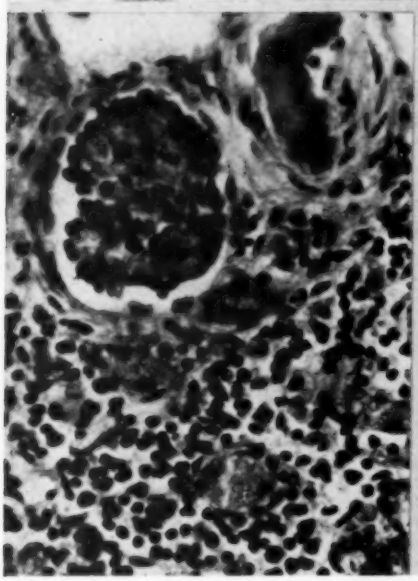
Gross and microscopic examination of the heart, alimentary tract, liver, pancreas, adrenals, testes, diaphragm, thymus, and salivary glands was essentially normal, except for generalized congestion and edema of moderate degree. The liver showed marked edema.

The lungs were the site of a generalized interstitial pneumonia. The pleural surfaces were smooth, dark reddish-purple posteriorly, and pale pink anteriorly. There was crepitation anteriorly, but a firm consistency in the posterior portions of all lobes. Section revealed flat, pinkish-red, dry surfaces. The trachea and bronchi contained a white, thick, mucoid

Fig. 1.

Fig. 2.





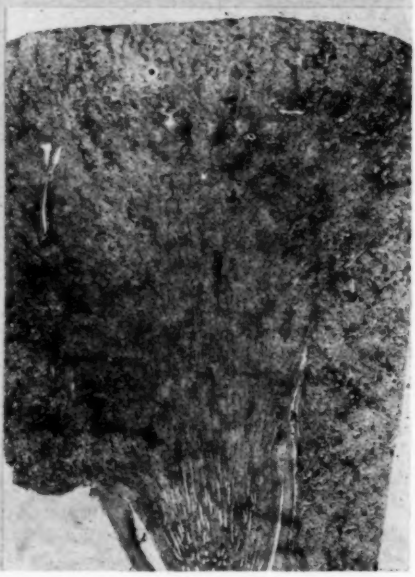


Fig. 3.

Fig. 4.

Fig. 1.—Right kidney and aorta showing radiating deposits of calcium in cortex and medulla. Arrow points to region of small plaques in aorta and iliac arteries.

Fig. 2.—Medium power view of kidney showing preservation of normal renal architecture of the glomeruli and proximal tubules, especially.

Fig. 3.—Focus of lymphocytic infiltration in cortex of kidney.

Fig. 4.—Low power view of kidney (von Kossa stain). Note preservation of general architecture. The dark staining material near the corticomedullary junctions represents calcium casts.

Fig. 5.

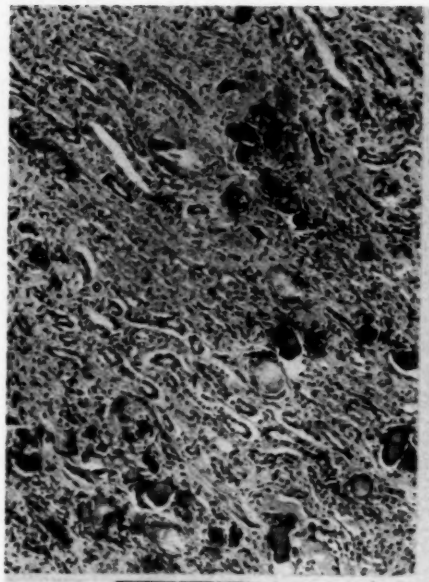


Fig. 6.

Fig. 7.

Fig. 8.

Figs. 5 and 6.—Low power views of kidney showing calcium casts and increased interstitial fibrosis.

Fig. 7.—Arrows point to parathyroids.

Fig. 8.—Arrows point to additional structures removed, two of which proved to be parathyroids.

Fig. 9. Fig. 10.

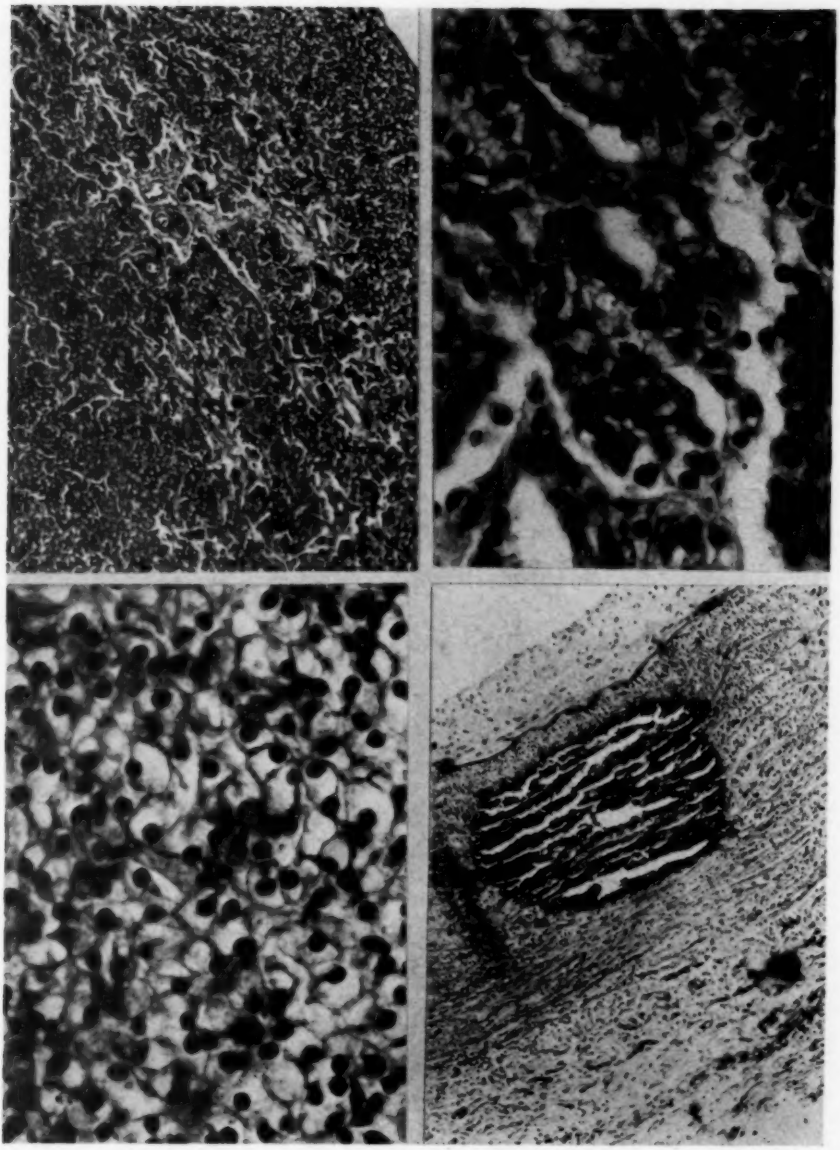


Fig. 11. Fig. 12.

Fig. 9.—Low power view of parathyroid showing dense cellularity.

Fig. 10.—High power view of normal parathyroid gland of patient aged 10 months, dying of hydrocephalus with complicating infections. Note the amount of stroma and looseness of cellular arrangement.

Fig. 11.—High power view of parathyroid showing the large number of chief and transitional water-clear cells and the compactness of the cellular arrangement.

Fig. 12.—View of aortic wall showing medial calcification.

Fig. 13.

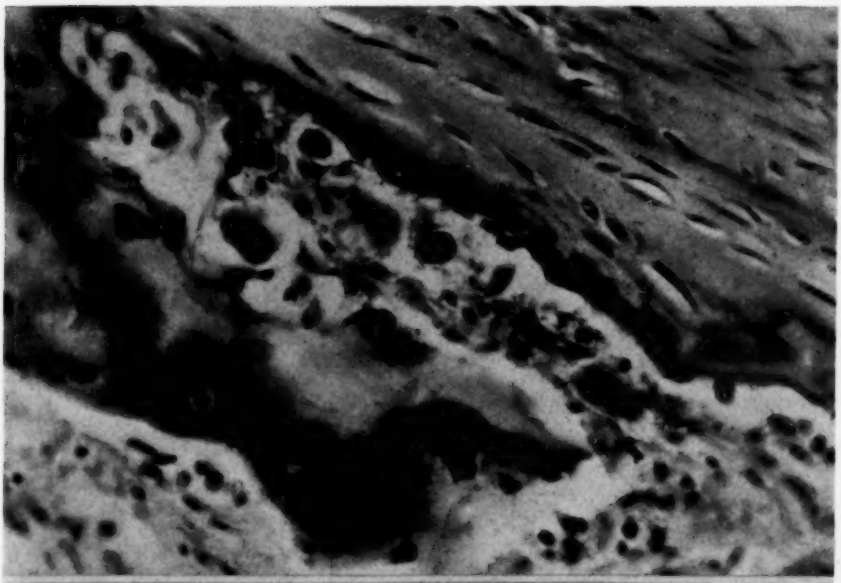


Fig. 14.

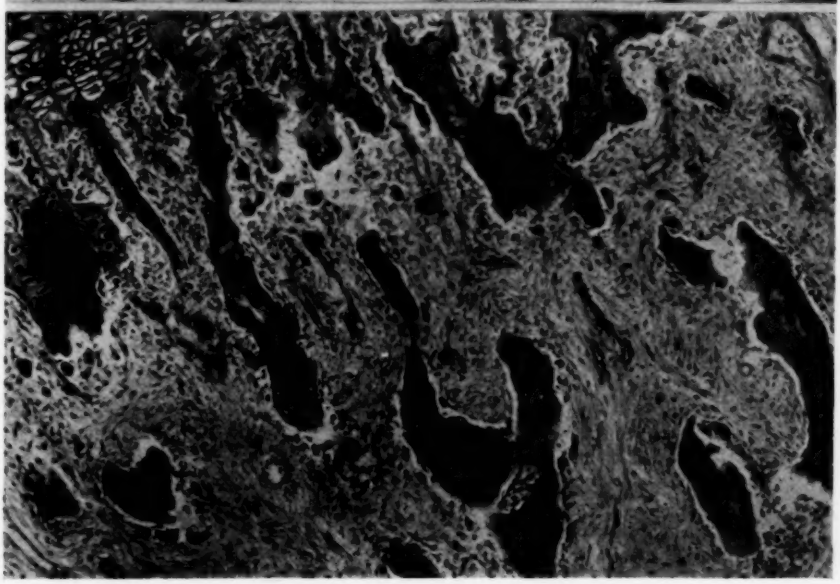


Fig. 13.—High power view of rib showing osteoclasts adjacent to cortical bone in shaft of rib.

Fig. 14.—Rib showing fibrosis of marrow spaces and increased numbers of osteoclasts.

material. The hilar lymph nodes were firm, pale red, and discrete. Microscopic examination showed generalized thickening of the alveolar walls, due to infiltration of large mononuclear cells and congestion of the capillaries. There were foci of emphysema and partial atelectasis. Most of the alveoli were empty, but a few contained ringlets of precipitated protein or small numbers of large mononuclear cells. Some of these mononuclear phagocytes contained brown granules of pigment in their cytoplasm. One section included a group of alveoli and a few bronchioles filled with extravasated red blood cells. There was marked edema of the interlobular, subpleural, and perivascular connective tissues. The capillaries and small vessels were markedly congested.

The malpighian corpuscles of the spleen, the mesenteric lymph nodes, and the lymphoid follicles of the large intestine showed the nonspecific changes of a marked toxic reaction with enlargement of the germinal centers and phagocytosis of cellular debris by the reticuloendothelial cells.

The most outstanding pathologic changes were seen in the parathyroids, kidneys, and skeletal system. The kidneys were enlarged. The capsules were thin and transparent. They stripped easily, revealing smooth, pale pinkish-red, external surfaces with shallow remnants of the fetal lobulations. The tubular markings on the surface were prominent as white foci averaging 0.15 cm. in diameter surrounded by thin, red, vascular markings. On sectioning the kidneys, there was a distinct gritty sensation. The cut surfaces bulged slightly and the corticomedullary junctions and tips of the pyramids were congested. Fine, white chalky lines radiated through the pyramids, medulla, and cortex, being especially numerous near the corticomedullary junction (Fig. 1). The calyces, pelves and ureters were patent and lined by a smooth, pinkish-gray, intact mucosa.

On microscopic examination, the general pattern of the renal architecture was preserved (Fig. 2). Most of the glomeruli appeared normal, but a very small number in each kidney showed one or more of the following changes: slight increased cellularity of the tufts; thickening of the layers of Bowman's capsule with crescent formation; and granular eosinophilic precipitate with occasional large mononuclear cells in the subcapsular spaces. Scattered through the interstitial tissues were small foci of infiltrated lymphocytes, plasma cells, and neutrophiles (Fig. 3).

The proximal convoluted tubules contained small amounts of granular, eosinophilic debris, except for a few which were greatly dilated with granular, grayish-blue casts. The loops of Henle contained small numbers of bluish casts that stained black in a von Kossa preparation (Fig. 4). Many of the collecting tubules contained similar large calcium casts. Some of the calcium was deposited around the tubules in the interstitial tissues, and a few calcium masses were seen in the walls of small arterioles in the cortex. The medulla and pyramids contained the greater part of the calcium. There was moderate to advanced increase in the interstitial fibrous tissue of the medullary regions (Figs. 5 and 6).

The parathyroid glands were grossly identified as small, pinkish, firm nodules along the lateral and posterior aspects of the thyroid gland (Figs. 7 and 8). On microscopic examination, all four glands were more cellular than normal and no stromal fat separated the cellular strands (Figs. 9 and 11). The predominant cell types were the chief cells and transitional water-clear cells[6] (Fig. 11).* A few small foci consisted of the large, water-clear cells. In scattered areas some of the cells showed nuclei arranged near the pole of the cell next to the stroma. Early attempts at pseudoacinar formation were seen. One cyst was noted containing granular, eosinophilic material and lined by chief cells. No oxyphileous cells were identified.

The only evidence of metastatic calcification was the presence of several small plaques of calcium deposited in the media of the abdominal aorta and iliac arteries (Figs. 1 and 12).

*Because of the conflicting terminology used in textbooks and articles concerning the histology of the parathyroid glands this note is added. Chief cell in this paper refers to the small cell with stainable cytoplasm that comprises the major portion of the gland. Transitional water-clear cell refers to a cell of the same size as, or slightly larger than, a chief cell, with a similar nucleus, but with clear and unstaining cytoplasm. Large water-clear cell refers to a cell that is much larger than the chief cell, has a similar nucleus, and no stainable cytoplasm. Oxyphile cell designates a cell with eosinophilic, cytoplasmic granules.

Microscopic preparations of the ribs revealed replacement of the hematopoietic tissue in the marrow spaces by collagenous tissue in which large numbers of osteoclasts and osteoblasts were identified (Figs. 13 and 14). The peripheral spaces were more densely replaced by fibrous tissue than the central marrow spaces, and in many places this fibrous tissue was continuous with the periosteum. Scattered foci of hematopoietic tissue were identified near the costochondral junctions, but became larger, hyperplastic, and more numerous farther from the junction. The lines of ossification were slightly irregular, with several columns of undegenerated cartilage cells extending beyond the zone of provisional calcification. Capillary penetration was fair.

An incidental finding was the presence of double ostia to the right coronary artery. No other congenital anomalies were noted.

COMMENTS

The outstanding abnormalities appeared to be an elevation of the serum concentrations of calcium and chloride, a decreased urea clearance, a low urinary excretion of calcium, diminished serum bicarbonate, hyperplasia of all four parathyroid glands due to increased numbers of chief and transitional water-clear cells (see previous footnote), nephrocalcinosis, and osteitis fibrosa.

The ionized calcium was increased as evidenced by the characteristic clinical symptoms, by the level of the spinal fluid calcium, and by calculation from the data in Table II. Since the serum inorganic phosphorus was usually below 4 mg. per hundred cubic centimeters, it should be regarded as abnormally low for the age of the patient.[7] The terminal episode which seemed to be an acute pneumonic infection, closely resembled the clinical and laboratory observations recorded from patients suffering from excessive amounts of parathyroid hormone.[3, 8] Only a single, short, metabolic balance period could be accomplished. In this period, when the intake was above that generally maintained by the patient and while vitamin D was omitted from the diet, the significant features were: the positive balances of calcium, phosphorus, and nitrogen, the relatively high ratio of calcium to phosphorus in the stools, and the small quantity of calcium in the urine. The photomicrographs show the predominantly chief and transitional water-clear cell structure of the parathyroid glands; the presence of calcium casts in the renal tubules with moderately increased interstitial fibrosis of the medulla and with preservation of most of the general renal architecture; and the replacement fibrosis of the marrow spaces with increased osteoblastic and osteoclastic activity.

DISCUSSION

The material presented poses several questions of importance to those interested in calcium and phosphorus metabolism. Did this disorder represent an instance of primary hyperparathyroidism in which the structure of the parathyroid glands differed from that previously accepted? If so, are these changes representative of primary hyperparathyroidism during infancy? Or was the fundamental disturbance one of secondary hyperparathyroidism which ceased to perform its service as a compensatory reaction and progressed to unbridled production of parathyroid hormone?

An attempt to clarify certain aspects of our observations will be made in the following paragraphs without the expectation that definite answers to the preceding questions can be reached from this study alone.

Excessive intake of vitamin D as a cause of this disorder seems to be excluded by the patient's course in relation to the intake of this vitamin.

Chown[9] reported two infants with hypercalcemia, nephrocalcinosis, and disturbances of the bones, and he postulated a primary diencephalopituitary lesion as the cause of the symptom complex. Although the brain and pituitary gland of our patient were not available for examination, the roentgenographic appearance and histologic structure of the bones in Chown's cases did not resemble our findings. Furthermore, Chown found no abnormality of the parathyroid glands in his patients.

The combination of impairment of renal function and enlargement of the parathyroids occurs most often as the result of primary renal disease. Chronic acidosis might lead to hypercalcemia because of the withdrawal of calcium from the bones, and both renal calcification and osteitis fibrosa have been associated with chronic acidosis.[10, 11] Nevertheless, we feel that renal damage was not the basic factor in this instance because of the practically stationary roentgenographic appearance of the bones, the failure of the hypercalcemia to be reduced when the acidosis was corrected by the administration of sodium bicarbonate, and the preservation of renal tissue on histologic examination. The ability of the kidneys to concentrate the glomerular filtrate, to produce ammonia, to alter the pH of the urine, and to maintain a normal value of nonprotein nitrogen and a low inorganic phosphate in the serum, all seem to oppose the hypothesis of primary renal damage.

The possibility that the basic disturbance was primary hyperparathyroidism is supported by the constancy and duration of the clinical symptoms, the progressive hypercalcemia, the frequently low serum inorganic phosphate, and the fact that the clinical picture seemed to fit no other disease.[12] Atypical features were the low urinary calcium output, the positive calcium and phosphorus balance, and the morphology of the parathyroid glands. Undisputed examples of primary hyperparathyroidism with low urinary calcium excretion have been reported. Secondary renal damage is said to account for the unexpectedly small output of calcium in the urine in such cases. In the present patient, the resorption of large amounts of calcium from the glomerular filtrate must have occurred in spite of the high level of serum calcium, because calculations utilizing the estimated diffusible calcium concentration in the serum and the urea clearance indicate that many times the amount of calcium found in the urine should have been present in the glomerular filtrate. The single determination of positive calcium and phosphorus balances might be explained either as a result of the high intake of these minerals in the usual diet for infants, or as representing a transient situation occurring during a period of slight clinical improvement. Similar studies while on a low calcium diet would be expected to reveal more pertinent information. These were contemplated, but could not be completed.

Effective treatment necessitates a more complete understanding of the physiologic disturbances than is available. Until more evidence is obtained, it would seem that prompt recognition of this condition, competent description of the disturbed physiology by means of carefully planned and rapidly executed studies, and then removal of a portion of the hyperactive parathyroid tissue would provide the greatest opportunitiy for survival, as well as for the acquisition of knowledge concerning the underlying process. The relatively rapid deterioration of the physical condition of our patient emphasizes the need for prompt recognition and study of such patients lest the opportunity for successful treatment be lost.

SUMMARY AND CONCLUSIONS

The clinical and laboratory investigations of a 10-month-old infant exhibiting extreme hypercalcemia, mild acidosis, impairment of renal function, and low urinary excretion of calcium have been presented. The post-mortem examination revealed chief cell hyperplasia of all four parathyroid glands, nephrocalcinosis, and osteitis fibrosa.

The apparently unique combination of hypercalcemia and chief cell hyperplasia of the parathyroids was not satisfactorily explained from our observations.

It is hoped some of the issues raised by this study will be solved by the investigation of similar patients.

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Photomicrographs made by John N. Carabitses.

BONE MARROW INFUSION IN CHILDHOOD

Experiences From a Thousand Infusions

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Copenhagen, Denmark

THE employment of bone marrow infusion was adopted almost simultaneously by various pediatric clinics in Denmark in the spring of 1943. We now have three to four years' experience in the employment of the method, and at the time of writing, in the summer of 1946, we have available data on close to 1,000 infusions given to 495 patients, the largest amount of information of this kind hitherto reported.

On the basis of this material we shall deal with several problems which, we think, have not been sufficiently discussed in the literature, and which have led to some misunderstandings, particularly in regard to the questions of technique and the risk of osteomyelitis.

The historical development of the bone marrow infusion has been mentioned in several papers. The suitability of the bone marrow for infusion was demonstrated as early as 1922 by Drinker and associates[13] and Doan.[12] At the Scandinavian Congress in Uppsala in 1933, Josefson[20] reported that in ten cases of pernicious anemia he had injected Campolon directly into the sternal marrow, and thought that he had obtained a good depot effect. In 1937, Benda and collaborators[7, 8] reported injections of bacteria as well as drugs and contrast media into the bone marrow. In 1940, Henning[18] published his paper on intrasternal transfusion; and in 1940-41, Tocantins[35] and Tocantins and O'Neill[36] reported their classical studies on bone marrow infusion.

In Denmark, blood transfusion via the bone marrow was first employed by Bang and associates[5] in 1942.

Through the following years, especially in the English literature, a number of reports have been published, in which practically all the authors who have employed the method to a fairly large extent recommend it and describe it as a great advantage in pediatrics.[1-4, 6, 9, 11, 14-17, 24, 27, 29, 32, 37-40] It is asserted more or less indiscriminately that substances suitable for intravenous injection could also be injected via the bone marrow. We wish to emphasize at once that we do not subscribe to this view, for reasons that will be given later. Even in their first paper, Tocantins and O'Neill[36] warned against the employment of hypertonic or other irritant solutions, a warning to which Wallden[41] recently has subscribed. The osteomyelitis literature will be reviewed in a subsequent section.

TECHNIQUE

The technique employed in the thousand infusions here discussed was developed by Køster.[21, 22] In our opinion, it represents the safest and, certainly, the simplest procedure described so far. In practically every case the infusion

From the University Clinic of Pediatrics and the Surgical Clinic C, the Rigshospital, and from the Queen Louise's Children's Hospital, Copenhagen.

is given in the ward with the child lying in his bed. The leg is fixed manually by a nurse; the surgeon merely washes his hands well, not as prior to an operation, and he wears no gloves or mask, as has been insisted upon by some authors.[1, 15, 24] Briefly, the procedure is as follows:

After the usual blood grouping and direct compatability test, the blood from the donor is withdrawn into a low, wide graduate (7 to 8 cm. in diameter). We have found the graduate of this size most practical, and we have used the addition of 1 part 3.80 per cent sodium citrate to 9 parts blood. After ordinary, thorough disinfection of the skin with iodine, the skin over the upper half of the tibia is tightened between two fingers, and the special bone-puncture cannula (Køster model, Fig. 1) is introduced by a light, boring motion in the middle of the anterior aspect of the tibia, about 3 cm. below the joint line, directed a little distally. One is never in doubt as to when the cortex is perforated. In only

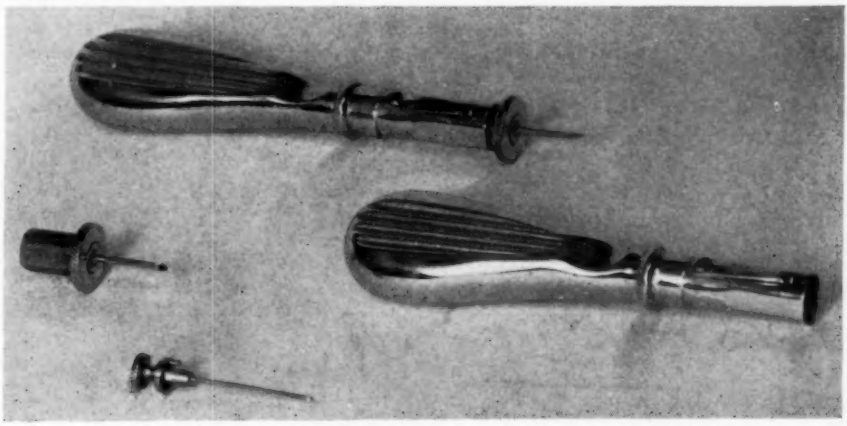

Fig. 1.—Køster model special bone-puncture cannula.

a few cases was local anesthesia applied beforehand (extending beneath the periosteum), as it is our impression that for children under 2 years this measure is quite superfluous and it made no difference in their reaction. On the other hand, in some cases of children over 2 years we have performed the puncture under slight ether anesthesia. After the introduction of the cannula, we make sure that it is situated in the free marrow space by means of aspiration with a 10 c.c. syringe, half filled with saline. This is of fundamental importance. (At this juncture some marrow may be aspirated for examination just as in ordinary sternal puncture.) After removing the syringe, a little blood and marrow will trickle out of the cannula if this is situated properly, showing that the cannula is free from air.

The transfusion is performed most conveniently by means of two 10 c.c. Record syringes, one being filled by an assistant while the blood in the other is being infused. The operator should, of course, make sure that the syringes contain no air.

Usually the infusion meets slight resistance, and this often subsides somewhat after infusion of the first 20 to 30 c.c. If, at this juncture, one feels more than a very slight, springy resistance, the cannula is not situated properly (it may, for instance, have entered one of the sides of the tibia), and its placing has to be corrected, preferably by introduction into the other tibia or into the distal part of the shaft of the femur. The same applies if oozing appears at the site of insertion, sometimes commencing with swelling of the subcutaneous tissue of the leg.

The maximal rate of infusion employed by us has been 10 c.c. per minute. And, as a rule, the infusion dose has been about 20 c.c. blood per kilogram of body weight.

CLINICAL MATERIAL

The present material is gathered from the following seven pediatric clinics in Copenhagen: The Blegdam Hospital (Epidemic), the Fuglebakken Children's Hospital, the Queen Louise's Children's Hospital, the Municipal Pediatric Clinic on Martinsvej, the Northern Hospital, the Pediatric Clinic of the Rigshospital, and the Pediatric Clinic of the Sundby Hospital.

The material comprises 495 patients who received a total of 982 bone marrow infusions in the period from the spring of 1943 to the spring of 1946, eighteen unsuccessfully.

The indications for the infusions will be evident from Table I, which gives the various diagnoses made.

TABLE I. DIAGNOSES OF PATIENTS WHO RECEIVED BONE MARROW INFUSIONS

DIAGNOSIS	NUMBER	DEATHS
Acute gastroenteritis with intoxication	338	127
Chronic dyspepsia	32	2
Fetal erythroblastosis	19	5
Pneumonia with complications	16	6
Meningitis	10	5
Anemia	8	1
Sepsis	8	6
Premature birth (congenital debility)	8	5
Leucemia	6	4
Tetanus neonatorum	5	3
Blood dyscrasias with hemorrhage	5	2
Hemorrhagic disease of the newborn	5	0
Various abscesses	4	3
Peritonitis	4	3
Congenital pyloric stenosis	4	0
Hemolytic anemia	3	0
Agranulocytosis	1	0
Various other diseases	19	7
Total	982	179

The group "various other diseases" comprises a number of different infectious diseases. As our material includes but a few patients with primary surgical illness, one of the most important indications, acute traumatic shock, is not represented here.

Many patients were given bone marrow infusion more than once, one patient as often as 10 times. Only in exceptional cases did the infusion fluid ooze out through the previous punctures. Continuous infusion was given to five

patients for up to thirty-two hours. Of these patients, four died under the infusion. The survivor contracted osteomyelitis (see below). The distribution of the total number of infusions follows:

Number Patients	*Number Infusions**
231	1
142	2
61	3
31	4
16	5
7	6
2	7
4	8
1	10

As a rule, infusions were not given at intervals shorter than two days, but they may very well be given at shorter intervals if necessary. Thus, in this series of cases, there were some patients who received five infusions within three days, and three of these infusions were given within twenty-four hours.

The youngest patient was 2 days old, the oldest, 4 years. The smallest patient weighed 1,200 Gm. In these extreme cases, the performance of the infusion met with no difficulty whatever.

The infusion fluids employed are listed in Table II.

As will be noticed from Table II, in several cases various remedies were given via the bone marrow. Particular mention is to be made of the injection of 50 per cent glucose, which was given to twenty-three patients in thirty-two infusions, as a rule in doses of 10 c.c.

TABLE II. INFUSION FLUIDS EMPLOYED

INFUSION FLUID	NUMBER INFUSIONS
Blood	686
Serum	174
Sodium bicarbonate	78
50 per cent glucose	32
Antitetanus serum	6
Perabrodil	3
30 per cent sodium sulfate	2
Calcium gluconate	1
Total	982

This form of treatment is not free from risk, as three of these patients (13 per cent) acquired osteomyelitis. The series includes two additional patients with osteomyelitis. These five cases will also be discussed later.

The infusion of serum has given rise to complications. The serum employed has been chiefly dry human serum, prepared by the State Serum Institute, Copenhagen. Beside the usual elements, the serum contains 5 per cent glucose. Specific antipneumococcus serum was employed in a few cases, and also scarlatinal convalescent serum.

Two patients died within twenty-four hours after intratibial administration of dry serum. The case histories of these two patients are as follows:

*Five of these patients were given continuous infusion.

CASE 1.—This patient was a 1-month-old boy, admitted for acute gastroenteritis with intoxication. As his condition remained poor, seventeen days after admission he was given 70 c.c. dry serum intratibially, without inconvenience. Twelve days later (twenty-nine days after admission), he had pronounced edema, for which he again was given 70 c.c. dry serum (29 c.c. per kilogram) intratibially, given in the course of fifteen minutes. About one hour later, he suddenly became exceedingly ill, shocked, pale, and cyanotic, with shallow respiration. In spite of stimulants, he died within one hour.

Autopsy diagnosis: perivascular cerebral hemorrhage, slight degree; diffuse pulmonary hemorrhages, recent and older; aspiration of meconium, slight degree; congestion of the spleen, slight degree.

CASE 2.—The patient was a boy, 16 days old, admitted for acute gastroenteritis with intoxication. On account of pronounced debility, on the day after admission the patient was given intratibial blood transfusion without inconvenience. One week later, moderate edema appeared. The patient was given dry serum intratibially (of the same lot of serum as given in Case 1), 35.7 c.c. per kilogram, without any immediate inconvenience. Ten hours later, the patient suddenly became listless, whining a little, with Cheyne-Stokes respiration and imperceptible pulse. At first he responded to stimulants, but an hour later he again became desperately ill and died in spite of stimulation.

Autopsy diagnosis: acute gastroenteritis; capillary bronchitis to a marked degree; bilateral atelectasis to a marked degree; congestion of the abdominal viscera.

In three additional cases the patients collapsed after serum infusion which had given no difficulty whatever, two of the patients about one hour after the infusion, the third about ten hours afterward. However, these children responded well to the stimulants given.

In eighteen cases the bone marrow infusion had to be recorded as a complete failure (1.8 per cent) as repeated attempts to enter a free marrow cavity failed in both tibias, or infusion of the fluid soon became blocked, after which the infusion was given up. Trouble of this kind may be due to the circumstance that the venous sinuses of the marrow, which afford the connection with the veins of the cortex (Meurling,[25]) have not developed sufficiently. On the other hand, it should be mentioned that it was possible to give an infusion to several patients a few days later without any difficulty whatsoever.

In spite of the relatively simple technique involved, the avoidance of such difficulties appears to be largely a matter of experience. Thus, it was found that in one hospital where 436 of the 1,000 infusions had been given, difficulties of this character were encountered in only twenty-six patients (in 6 per cent as against 9.9 per cent for the rest of the cases).

In 8.2 per cent of the patients the infusion did not proceed smoothly but it was still carried through, mostly by changing from one tibia to the other. The troubles most often encountered have been difficulties in entering a free marrow cavity. In other cases a considerable hematoma has formed at the site of the injection, causing swelling of the entire extremity in one patient. In some cases a hematoma has formed on the posterior aspect of the leg, signifying that the cannula has been forced straight through the tibia. Finally, mention is to be made of occasional technical difficulties such as bending of the needle, and sticking of the piston in the syringe.

None of the last-mentioned minor difficulties gave any lasting inconvenience.

Thus it is to be pointed out that 686 intratibial blood transfusions were given with this technique, without any serious complication whatsoever, whereas injection of hypertonic fluid and permanent infusion have given serious complications.

HISTOLOGIC EXAMINATION

Even though injection of contrast media has shown that, as far as absorption is concerned, intraosseous injection fully comes up to the level of intravenous injection, the idea still suggests itself that the bone marrow infusion might bring about some injury to the proximal tibial epiphysis. This is not the case, however. In eleven patients who died within fourteen days after the infusion, the respective tibiae were removed for examination. The only macroscopic finding was the site of the insertion of the needle, about as thick as a pin. In no specimen was any abnormal feature seen to arise from this site. In every specimen the epiphyseal line was found to be perfectly normal microscopically.

ROENTGENOLOGIC EXAMINATION

Even though the histologic examination revealed nothing suggestive of any injury to the epiphyseal line, and even though clinical control with an observation period of over three years for the first treated patients in no instance has disclosed any disturbance of the growth, we still found it to be of great interest to investigate, through systematic roentgenologic control, whether there might be any demonstrable, permanent, roentgenographic changes in the tibia after a considerable length of time. This seemed desirable, as some authors have reported roentgenologic changes in the form of noticeable drilling holes and periosteal reactions in immediate connection with the infusion.[10, 33, 41]

Of our 495 patients, seventy-two were examined roentgenographically as follows:

I: 36 patients were examined 0 to 1 year after the infusion.
II: 18 patients were examined 1 to 2 years after the infusion.
III: 18 patients were examined over 2 years after the infusion.

Group I.—A majority of these patients were examined within six months after the transfusion. In the first weeks after the transfusion, several of the examinees showed noticeable sites of puncture, a little over pin-head size, with slight, though unquestionable, marginal sclerosis. In our series this phenomenon was demonstrated in six patients, but it was never observed more than six months after the infusion, and as a rule it seemed to disappear much sooner. Two patients who had been given eight and four intratibial transfusions respectively, presented a slightly irregular structure of the proximal end of both tibiae. Another patient had been given four transfusions within seven weeks, each time with difficulty, as each time it proved necessary to change from one tibia to the other. At one attempt, a hematoma of the right leg appeared. Fig. 2 shows sites of puncture with sclerosis and slight structural changes in the proximal part of the metaphysis of the right tibia. In addition, there are distinct, periosteal deposits that presumably can be interpreted as evidence of a rather considerable subperiosteal hematoma.

Thus it may be looked upon as established that simple blood transfusion via the bone marrow in a certain, relatively small number of patients gives rise to slight roentgenographic changes. The significance that is to be attached to these changes will be evident from Groups II and III.

Groups II and III.—These two groups, which represent the real follow-up examination, gave an indisputable result: none of the thirty-six patients, who were picked out quite at random, showed any roentgenologic abnormality, and in every instance the growth of the bone had proceeded normally on both sides. This outcome is the more significant when we consider that the eighteen patients with an observation period of over two years received their transfusion at a time when the experience in the technical procedure was not as great as later on. Furthermore, in one of these patients a considerable subperiosteal hematoma had appeared immediately after the transfusion; and, as mentioned above, in several cases the attempts at transfusion had failed in part.

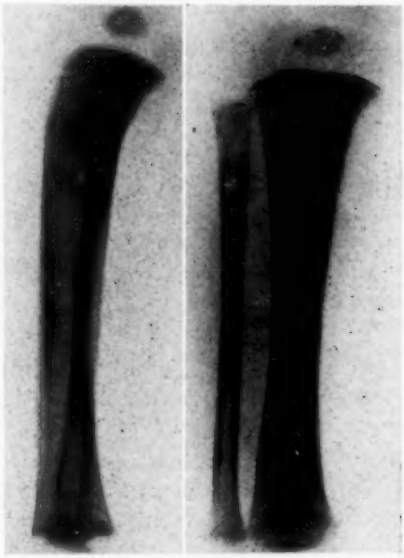

Fig. 2.—Roentgenogram of patient in Group I, showing sites of puncture with sclerosis and slight structural changes in the proximal part of the metaphysis of the right tibia. Distinct periosteal deposits can be interpreted as evidence of subperiosteal hematoma.

The result of the x-ray examination may be summed up to this effect: simple blood transfusion via the tibial bone marrow may sometimes give transitory, but not permanent, roentgenologic changes, and thus should not disturb the growth of the bone.

OSTEOMYELITIS

The only serious complication that may arise from bone marrow infusion is osteomyelitis. In the literature accessible to us, only a few instances of the

complication have been mentioned, and we have found no attempt to estimate how serious this complication may be. The patients we have found reported in the literature are listed in Table III.

TABLE III. OSTEOMYELITIS FOLLOWING BONE MARROW INFUSION: PATIENTS REPORTED IN LITERATURE

AUTHORS	NUMBER INFUSIONS	PATIENTS WITH OSTEOMYELITIS
Behr[6]	40	1
Gunz and Dean[15]	35	3
Quilligan and Turkel[29]	45	1
Rooney[33]	100	2
Tocantins, Price, and O'Neill[40]	79	3

Behr's patient had been given continuous intratibial infusion. The osteomyelitis yielded promptly to surgical treatment.

In two of the three cases reported by Gunz and Dean[15] the patients had been given blood transfusions, and on this account the authors feel justified in advising against infusion of whole blood. No mention is made of the clinical course of the three cases; all three patients had been given continuous infusion.

In the case reported by Quilligan and Turkel[29] the patient was given intratibial infusion for four days on account of peritonitis and, possibly, sepsis. Autopsy two days later revealed an extensive inflammatory process comprising practically the entire bone marrow.

The two patients reported by Rooney[33] had osteomyelitis after continuous infusion. In one, the inflammation was localized at the proximal end of the tibia, in the other, at the distal end of the femur. The first patient was admitted for operative treatment; in the other, a subcutaneous abscess was incised. Both recovered and after five months no deformity could be discovered.

Details in the three cases reported by Tocantins, Price, and O'Neill[40] are unknown to us, as we have had no access to the original paper.

Reisman and Tainsky[31] mention a patient who had a subcutaneous abscess at the site of puncture after a blood transfusion via the bone marrow; the abscess perforated spontaneously. X-ray examination three months later showed pronounced periosteal bone formation at the level of the previous abscess formation, but no destruction of bone. In this case the lesion may hardly be recognized as osteomyelitis.

In our material we have seen five instances of osteomyelitis, the records of which will be given briefly:

CASE 1.—A boy, born Sept. 29, 1944, was admitted to Fuglebakken Children's Hospital, Oct. 6, 1944. The diagnosis was premature birth and acute gastroenteritis with intoxication.

Weight at birth was 2,100 Gm. On August 11, the child was extremely exhausted, and continuous intratibial infusion was given on the left side for thirty-two hours (220 c.c. serum plus 50 c.c. saline). Five days later, there were edema of the left leg and discharge of pus from the site of the puncture. X-ray examination on November 23 showed a rarefaction in the proximal metaphysis. After chiseling, the osteomyelitis lesion healed in two months.

Re-examination at the age of 14 months showed shortening of the left leg amounting to 1 cm., and atrophy of the calf amounting to 0.5 cm. in circumference. The left knee was lacking 10 degrees in complete extension, and there was 10 degrees varus position. Roentgenographically, the structure of the tibia was irregular proximally, with absence of the epiphyseal nucleus. The left tibial diaphysis was 0.5 cm. shorter than the right.

CASE 2.—A boy, born April 18, 1945, was admitted to the Pediatric Clinic of the Rigshospital on May 29. The diagnosis was premature birth, edema, and glioma of the retina.

Weight at birth was 1,150 Gm., weight on admission was 1,750 Gm. On the day before admission the patient was given 10 c.c. of a concentrated serum solution (corresponding to about 40 c.c. normal serum) in the right tibia. Four days later the entire right leg was swollen, with discharge of pus from the site of the puncture. X-ray examination on June 25 showed extensive osteomyelitis with large osseous abscesses in the metaphyses and total necrosis of the entire diaphysis, which was enveloped by a vigorous sequestral capsule. Under surgical treatment the osteomyelitis healed in one month. The patient died at the age of five months from an intercurrent infection.

CASE 3.—A boy, born Nov. 25, 1945, was admitted to Queen Louise's Children's Hospital on November 29, 1945. The diagnosis was acute gastroenteritis with intoxication.

Weight at birth was 1,750 Gm. On Feb. 3, 1946, the patient was given an infusion of 10 c.c. 50 per cent glucose into the bone marrow of the left tibia, followed by saline. On the next day the entire leg was swollen, and a few days later there was secretion from the site of puncture. On Feb. 15, 1946, there was increasing swelling and more profuse secretion from the fistula. X-ray examination on March 2 showed progressive osteomyelitis, and, on March 12, extensive destruction of the proximal metaphysis and vigorous periosteal formation of bone round the entire diaphysis. From March 14 to April 15, the patient had oscillating temperature, with no other demonstrable cause. In response to penicillin therapy the fistula closed, and the inflammatory process subsided. On May 1 both legs appeared perfectly normal; there was no clinical evidence of osteomyelitis.

Re-examination on Sept. 12, 1946, showed 1 cm. shortening of the left leg. On x-ray examination the epiphyseal line was shown to be almost effaced, the zone of ossification irregular, and the metaphysis broadened.

CASE 4.—A male child, born Dec. 2, 1944, was admitted to Queen Louise's Children's Hospital on Dec. 14, 1945, with a diagnosis of acute gastroenteritis with intoxication.

Weight at birth was 3,740 Gm., and weight on admission was 2,700 Gm.

On Jan. 16, 1946, the patient was given an infusion of 20 c.c. 50 per cent glucose into the marrow of the left tibia. Seven days later there was swelling of the entire left leg and secretion of thin pus from the site of puncture. X-ray examination on Feb. 4 showed typical osteomyelitis. On March 4 it showed extensive destruction of the entire proximal metaphysis, and strong periosteal reaction, corresponding to the entire diaphysis. April 3, after treatment with penicillin, a defect was seen in the proximal epiphyseal nucleus of the left tibia and a similar defect in the corresponding metaphysis. The epiphyseal line was indistinct and broadened. There was no distinct difference in the length of the two legs. On discharge from the hospital, the mobility of the legs was normal. The left tibia was a little thicker than the right, but otherwise there were no abnormalities.

Re-examination on Sept. 12, 1946, showed no clinical abnormality. X-ray examination showed a slightly irregular epiphyseal line.

CASE 5.—A girl, born Nov. 20, 1945, was admitted to Queen Louise's Children's Hospital November 24 with a diagnosis of acute gastroenteritis with intoxication.

Weight at birth was 2,650 Gm. The child was extremely exhausted, and on November 26, because of edema of the brain, was given a bone marrow infusion of 10 c.c. 50 per cent glucose in the left tibia. Seven days later the entire left leg was red and swollen. X-ray examination on December 19 showed extensive osteomyelitis with focal destruction of the proximal metaphysis, a nut-sized area of rarefication in the distal part of the diaphysis, and total necrosis of the entire diaphysis, which was enveloped by a vigorous sequestral capsule.

Under treatment with hot compresses and sulfathiazole the process became quiescent. On Feb. 28, 1946, no demonstrable abnormality of the left leg could be made out. One month later the patient died of an intercurrent disease.

Our series includes no instance of subcutaneous abscess formation, nor have we observed any instance of fat embolism as described by Wile and Schamberg.[42]

As is evident from the case histories above, the five instances of osteomyelitis arose in connection with (1) continuous infusion (Case 1), and (2) simple infusion of hypertonic solutions, namely, concentrated serum (Case 2), and 50 per cent glucose (Cases 3 to 5).

In the 944 bone marrow infusions of isotonic solutions (blood, serum, and bicarbonate) with employment of Køster's technique, osteomyelitis was not observed in any patient, in spite of the fact that many of the patients were extremely exhausted and, consequently, highly susceptible to infection.

In the future, a sharp distinction must be made between the risk of osteomyelitis after the simple infusion of isotonic fluids in one seance as given by Køster, and the risk after continuous bone marrow infusion and infusion of hypertonic fluids, which in our material has been about 13 per cent.

This conclusion, we think, is the important finding of our study.

The risk implied by continuous bone marrow infusions is evident from the osteomyelitis literature cited, as in all the cases quoted the osteomyelitis developed after continuous infusion.

Attention has been called from other sides to the irritative effect of the hypertonic solutions. Experimentally, Wallden[41] has demonstrated roentgenographic changes after such infusions, and Christiansen[10] has seen rather considerable periosteal reactions after bone marrow infusions of undiluted contrast media.

CONCLUSION

It is generally agreed that blood transfusion performed on the proper indications is one of the most valuable therapeutic measures available. Infusion into the cubital, saphenous, cervical, or cranial veins is often difficult for experienced physicians; and even with the employment of certain technical tricks (Landman[23] and Isotalo[19]) it is often impracticable without laying the vein bare. Infusion into the longitudinal sinus is a measure about which the inexperienced physician always will feel uneasy. (In going through about half a hundred case records where this form of infusion was employed, we have found two cases in which a subdural hematomata developed, one of which required operative treatment.)

According to our experience, there can be no doubt whatever that the introduction of the technique of bone marrow infusion in pediatrics has been of valuable significance.

On the other hand, however, as already pointed out by Tocantins and O'Neill[36] in their first paper, and more recently emphasized by Wallden,[41] it has to be kept in mind constantly that bone marrow infusion is not meant to replace intravenous infusion. It is a supplementary method, and it should be reserved for patients in which the intravenous way is not suitable, as is often

true in children. Even though the bone marrow route absorptionally is analogous to the intravenous, intraosseous injection of the same substances may involve a considerable risk.

We think the most important result of the present study has been that it now seems quite evident that we have to distinguish sharply between the ordinary simple blood transfusion or infusion of isotonic solutions in one seance, which has proved to be quite safe so far, and the continuous infusion, or the infusion of hypertonic solutions that implies a considerable risk of osteomyelitis and subsequent disturbance in growth of the bone.

Consequently, we do not hesitate to employ the bone marrow infusion for simple blood transfusion in infancy. In about 10 per cent of the cases, however, there will be technical difficulties in placing the cannula properly, but only in 2 per cent of the cases will these difficulties be so great as to make the transfusion altogether impossible. Furthermore, we have never seen any unfortunate consequences from unsuccessful attempts at transfusion in this way.

When it comes to continuous infusion, the requirements as to aseptic and antiseptic precautions, technique, and apparatus will be far more exacting. The infusion fluid must be kept absolutely sterile, and there must be no possibility of airborne infection. These requirements are met by the English "Transfuso-Vac" system[2] and the apparatus constructed by Price and Tocantins,[28] just to mention a couple of examples. We have had no personal experience with these measures, but we find it advisable never to extend a continuous infusion beyond twenty-four hours (Køster, private communication).

As to the injection of hypertonic solutions via the bone marrow, we are decidedly against the employment of this measure. The only exception to this rule must be a vital indication under circumstances affording no possibility of laying a vein bare, e.g., in manifest edema of the brain or far advanced hypoglycemia. We also wish to remind that bone marrow infusion of hypertonic solutions is associated with very intense pain (Meyer and Perlmutter[26]), probably as a sign of tissue injury. Presumably it is through this tissue injury that ubiquitous bacteria, which usually are completely or partly apathogenic, have a possibility of exerting a deleterious effect, resulting in osteomyelitis.

We have emphasized these facts in order to contribute toward keeping the simple bone marrow transfusion, which offers great advantages in infancy, from falling into discredit. No dangerous, let alone fatal, complications have been observed in connection with its employment.

SUMMARY

1. Material is presented, on nearly 1,000 bone marrow infusions given to children, aged 0 to 4 years, chiefly to infants. The character of the material, frequency of infusions, and the fluids injected are shown in Tables I and II. The very simple technique is described in detail.

2. Histologic examination of the tibia, performed on eleven patients from one to fourteen days after bone marrow infusion, showed no abnormality, especially no damage to the epiphyseal line.

3. X-ray examination of the tibiae, performed on thirty-six patients from one to two years after bone marrow infusion, showed no abnormality of the bones.

4. According to our experiences from 686 infusions, ordinary simple blood transfusion via the bone marrow at one time is quite safe, as we never have seen it followed by any serious complication, let alone osteomyelitis.

5. Continuous infusion, or infusion of hypertonic solutions, implied a considerable risk of osteomyelitis. Five instances of this complication are reported.

6. In our opinion, the failure to emphasize these facts in the literature is likely to place the employment of blood transfusion via bone marrow in infancy in a false position.

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THE ESTIMATION OF EXTRACELLULAR AND TOTAL BODY WATER IN THE NEWBORN HUMAN INFANT WITH RADIOACTIVE SODIUM AND DEUTERIUM OXIDE

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TRACER techniques have been used frequently for estimation of extracellular and total body water. In adult man there are extensive observations on the volume of extracellular fluid determined from the distribution of sodium tagged with its radioactive isotope,[1] and there is a single observation on the volume of total body water determined from the distribution of deuterium oxide.[2] We have been unable, however, to find any data of this kind for the newborn human infant. In addition to giving us essential information for current studies on the permeability of the human placenta, our observations, though limited to three cases, give consistent answers to the questions: what proportion of the body weight in the newborn is water and how much of this water is extracellular?

Sodium chloride, tagged by radioactive sodium (Na^{24}) at intensities of radiation below those known to produce measurable biologic effects, was dissolved in water containing deuterium oxide (D_2O) and injected into a scalp vein of three newborn human infants. Two and one-half to three hours later, samples of oxalated blood for analysis were obtained by internal jugular puncture. This period of time is sufficient for equilibration of heavy water (DHO) in blood with extravascular water.[2] It is not sufficient for complete equilibration of injected sodium in adult man, but further time up to six hours after injection[1] results in an increment of volume of distribution which for our purposes is unimportant. Radioactivity of the plasma fraction of the blood was measured by a temperature-controlled, pressure ionization chamber connected to a string electrometer. These measurements were corrected for the error due to self-absoption of radiation by the wet plasma sample.[3] The water of the blood for measurement of its deuterium content was obtained by vacuum distillation to dryness. Purification of this water and the method of determining the concentration of heavy water by the falling drop method were as described by Keston, Rittenberg, and Schoenheimer.[4] The volumes of distribution of the injected sodium and deuterium oxide (Na-space or DHO-space) were determined from the formula:

$$V_2 = \frac{C_1 V_1}{C_2}$$

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where C_1 and V_1 are the concentration and volume of the substance intravenously injected, C_2 the concentration at the end of two and one-half to three hours in plasma, if for sodium, or in the water extracted from whole blood, if for heavy water, and V_2, the final volume of distribution of the tracer in the subject. As is customary, V_2 is expressed as per cent of body weight on the assumption that the density of the fluid of V_2 is unity. The concentration of tagged sodium in plasma was obtained from the measured radioactivity, 1 mg. of sodium in these experiments having a radioactivity of 2.43×10^5 counts per second. In the case of tagged sodium, no correction was made for water content of plasma, for sodium bound in the plasma, or for the Donnan effect.[1] Evidence that a satisfactory measure of total body water is obtained from the experiments with deuterium oxide has been reported by Moore,[2] who found good agreement in the rabbit between the values derived from deuterium oxide and those obtained by desiccation of the carcass.

Results are given in Table I. The average value of 74.6 per cent of body weight for total body water differs only slightly from that of 72.5 per cent reported for a single adult male by Moore[2] using the tracer technique and 75.5 per cent found by Iob and Swanson[5] by desiccation of a full-term human infant. Utilizing the data of Iob and Swanson[5] on the chloride content of a human infant at term, and assuming that chloride is almost completely extracellular, Harrison, Darrow and Yannet[6] have calculated the extracellular water to be 43 per cent of the body weight. This is in excellent agreement with the average value of 43.5 per cent obtained two and one-half to three hours after injection of labeled sodium, and indicates that choice of this period of time after injection in the newborn avoids relatively large distortion of the value for extracellular fluid due to penetration of labeled sodium into bone.[6, 7]

TABLE I

SUBJECT	AGE (DAYS)	WEIGHT (GM.)	Na^* INJECTED (MG.)	C.C. 96% D_2O INJECTED	Na^* PER C.C. PLASMA (MG.)	% DHO IN PLASMA WATER	% BODY WEIGHT	
							Na^*-SPACE	DHO-SPACE
Baby C	6	3,990	7.14	6.0	0.00412	0.195	43.5	73.8
Baby E	7	3,010	4.48	5.0	0.00322	0.208	46.2	76.8
Baby S	1.5	2,920	4.48	5.0	0.00376	0.222	40.8	73.2
	Average						43.5	74.6

Na^* refers to sodium tagged with radioactive sodium. The values for Na^* per cubic centimeter plasma and per cent of heavy water in plasma water were obtained on samples secured two and one-half to three hours after injection.

Considerable evidence is now at hand that the process of growth is accompanied by an increase in the ratio of the intracellular to the extracellular phase. Extracellular water in adult man, as determined with tagged sodium three hours after intravenous injection, constitutes 25 per cent of body weight.[1] The sodium-space in relation to body weight, as determined in these experiments, is 1.7 times as large in the newborn as in the adult, and constitutes 58 per cent of total body water in the newborn as compared to 35 per cent in the adult. Harrison, Darrow and Yannet,[6] using the chloride analyses by Iob and Swan-

son,[5] found that the extracellular fluid in the human fetus during the fifth month of pregnancy amounts to 62 per cent of body weight and that this value progressively decreases to term. Much the same results were obtained with the fetuses of guinea pigs using radioactive sodium;[3] the sodium-space two-thirds through gestation approximates 60 per cent of body weight and falls to about 30 per cent at term. Yannet and Darrow[8] in their study of tissues of the growing cat also observed a decrease in extracellular fluid volume from the fourth to the sixth month of postnatal life.

SUMMARY

On the basis of dilution of a known quantity of intravenously injected sodium chloride tagged with a radioactive isotope of sodium, the extracellular fluid volume in three newborn human infants has been found to average 43.5 per cent of the body weight. Similar measurements with deuterium oxide gave a volume of total body water equal to 74.6 per cent of body weight.

We are obliged to the Abbott Laboratories for a grant for purchase of the heavy water.

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RENAL GLYCOSURIA ASSOCIATED WITH PENTOSURIA

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IT BECOMES apparent that the presence of a reducing substance in the urine must be considered critically when it is realized that one out of every six persons with a melituria suspected of diabetes is ultimately proved to have a benign condition.[1] It is unsafe, however, to assume that glucose is the actual cause of a positive reduction test, especially when the concentration of the reducing substance is less than 1 per cent, unless glucose is definitely identified. Demonstrating glucose should not exclude the possibility of a combination of two or more sugars existing concomitantly. An instance of renal glycosuria associated with intermittent pentosuria occurring together in the same patient presenting diabetic symptoms is being reported, accordingly, as a case in point.

CASE REPORT

E. G., a 5-year-old Negro boy, was admitted to The Children's Memorial Hospital for study of a persistent melituria first noted at 26 months of age. The patient, one of three siblings, had been well except for a history of pertussis, varicella, exposure to tuberculosis, umbilical hernia, and hydrocele. There was no known family history of diabetes mellitus. There was nothing to suggest hepatic disease, hyperfunction of the endocrines, increased intracranial pressure, alkaptonuria, convulsions, or the prolonged use of drugs. The course had been benign although punctuated by a craving for sugar, polydipsia, and polyuria. Melituria, presumed to be a glycosuria, was almost constantly present, though occasional urine specimens taken before breakfast were free of sugar. Frequent quantitative determinations for reducing substances taken during the patient's observation in the outpatient department had varied from 0.16 to 0.77 per cent, the lower values occurring uniformly in the morning in a usual range of from 0.2 to 0.3 per cent. Active fermentation of afternoon urine specimens was the rule, though morning specimens often failed to evidence fermentation, even in the presence of reducing substances in a 0.2 to 0.3 per cent concentration. Acetone and diacetic acid were never demonstrated.

The dietary history was pertinent and revealing. The child ate cherries for breakfast daily during the months of June through December and was quite fond of plums, grapes, and berries, which were alternated at the morning meals during the rest of the year. Alterations in the diet with restriction of carbohydrate had been tried, moderately affecting the quantitative afternoon sugar excretion. The fruits noted, however, had never been eliminated from the diet.

Physical examination at the time of admission to the hospital revealed an alert, asymptomatic child, 43 inches in height and weighing 48 pounds. Aside from evidence of repair of an umbilical hernia and hydrocele, no abnormalities were demonstrable.

Laboratory Observations.—The blood count was normal. Reactions to an Eagle and Mantoux test (1-1,000 dilution) were negative. Analysis frequently repeated on several days revealed that the urine was normal except for a positive qualitative Benedict's reaction (1 to 3 plus) with quantitative values ranging from 0.25 to 0.75 per cent. Acetone and diacetic acid were never present. Postcibal morning specimens were negative when the fruits noted were eliminated from the breakfast meal.

Positive phloroglucinol-hydrochloric acid tests and positive orcin tests (Bial's modification) were obtained from urines excreted following a breakfast containing pentoses in moderate quantity. This phenomenon was not evidenced by other children on a similar

From The Children's Memorial Hospital, Chicago.

diet. Negative Rubner, Seliwanoff, and mucic acid tests of the urine were obtained. Characteristic pentosazones were obtained with the phenylhydrazine test.

An oral dextrose tolerance test, using 1.75 Gm. of dextrose per kilogram of body weight, yielded the following blood sugar levels after fasting (12 hours) and in one-half hour, one, two, and three hours respectively: 79, 117, 106, 98, and 83, mg. per 100 c.c. of whole blood. Urine samples collected just before drawing each blood sample were negative for reducing substances except at the end of one hour, when a 2 plus qualitative (0.5 per cent quantitative) Benedict's reaction was obtained.

An intravenous dextrose tolerance test[2, 3] revealed the following capillary blood sugar levels after fasting (12 hours) and in one-half, one, and two hours respectively: 103, 129, 96, and 113, mg. per 100 c.c. of whole blood. Urine specimens collected before drawing each blood sample were sugar free except at one-half hour, when a 0.75 per cent quantitative reduction of Benedict's solution was obtained.

A pentose tolerance test, using 1.75 Gm. per kilogram of technical d-xylose was done.[4] At the intervals noted, 5 c.c. of blood were obtained by venipuncture and collected in oxalate bottles. The total blood sugar was determined by the Folin-Wu method. The nondextrose reducing substance was determined by the same method, removing fermentable sugar by fermentation in washed yeast cells.[5] The total blood sugar minus the nondextrose reducing substance represents dextrose. The pentose is derived as the difference between the fasting value for nondextrose reducing substance and subsequent values for nondextrose reducing substance obtained after pentose administration. The results are given in Tables I and II.

TABLE I. PENTOSE TOLERANCE TEST

TIME (HR.)	TOTAL SUGAR (MG./100 C.C.)	NON-DEXTROSE REDUCING SUBSTANCE (MG./100 C.C.)	DEXTROSE (MG./100 C.C.)	PENTOSE (MG./100 C.C.)	URINE VOLUME (C.C.)	PER CENT REDUCING SUBSTANCE IN URINE
Patient						
Fasting	95	15	80	0	75	0.1
½	122	48	74	33	15	0.3
1	145	65	80	50	15	1.6
2	166	84	82	69	37	5.0
3	130	64	66	49	38	4.5
Control						
Fasting	86	21	65	0	80	–
½	133	44	89	23	90	<0.1
1	169	70	99	59	20	0.13
2	190	92	108	71	67	0.14
3	200	90	110	69	110	<0.1

TABLE II. DIFFERENTIAL VALUE OF USUAL TESTS FOR IDENTIFICATION OF URINARY SUGARS*

TESTS	GLUCOSE	GALACTOSE	LACTOSE	FRUCTOSE	PENTOSE	GLYCURONATES
Benedict's	+	+	+	+	+	+
Fermentation	+	Occasionally, slowly	–	+	–	–
Bial's orcinol	–	–	–	–	+	+
Rubner's	–	–	+	–	–	–
Seliwanoff's	–	–	–	+	–	–
Mucic acid	–	+	+	–	–	–
Phloroglucinol	–	–	–	+	+	+
Naphthoresorcinol	–	–	–	–	–	+

*The following chart is appended to indicate the differential value of the usual qualitative tests for identification of urinary sugars. The significance of the reactions elicited in the case being presented becomes more clear as reference is made to the chart. Positive and negative reactions are indicated by + and – respectively.

Control values were obtained from a child weighing 52 pounds. A dextrose tolerance test using 1.75 Gm. dextrose per kilogram of body weight yielded the following fasting (12 hours), one-half-, one-, and three-hour blood sugar values in terms of milligrams per 100 c.c. of whole blood: 86, 123, 120, 102, and 104. The urine specimens obtained concomitantly at the same intervals of time were negative for reducing substances. The nonprotein nitrogen was 33 mg. and the urea nitrogen 15 mg. per 100 c.c. of blood. The pentose tolerance curve using 1.75 Gm. per kilogram of body weight of technical d-xylose yielded the values noted.

Other chemical determinations of the patient's blood were as follows: The nonprotein nitrogen was 29 mg., the urea nitrogen, 13 mg., creatinine, 1.1 mg. per 100 c.c. of whole oxalated blood. Other values per 100 c.c. of serum were calcium, 10.6 mg.; phosphorus, 3.4 mg.; phosphatase, 8 Bodansky units; cholesterol, 188 mg.; cholesterol esters, 94 mg. The bromsulfalein test, using 5 mg. of bromsulfalein per kilogram, revealed less than 5 per cent of the dye in the serum after 30 minutes. An intravenous pyelogram revealed normal findings.

DISCUSSION

The most frequent single disease entity characterized by glucosuria is diabetes. Diabetes mellitus is responsible, however, for only 30 per cent of clinical glycosurias in children.[6] Hyperglycemic glycosurias other than diabetes should, therefore, be given their due consideration. Hyperfunction of some of the endocrine glands (thyroid, pituitary, adrenals), chemical agents, hepatic and renal disease, acidosis, asphyxia (caused by anesthetics, shock, convulsions) and increased intracranial lesions or pressure should all be borne in mind. Normoglycemic glycosurias should suggest renal glycosuria and the clinically significant meliturias other than glycosurias, including the excretion of the disaccharides, lactose and maltose, and the monosaccharides, galactose, levulose, and pentose.

A variety of nonsugar reducing substances is demonstrable in human urine. Uric acid, nucleoprotein, creatinine, formaldehyde, and chloral reduce Fehling's solution, though their effect is less appreciable on Benedict's qualitative solution. Ascorbic acid in large dosage and homogentisic acid of the alkaptonuric reduce copper salts. Glycuronic acid, a conjugating substance in the detoxifying mechanism of the liver complementing hippuric acid and sulfate formation, constitutes a not uncommon urinary reducing substance. Glycuronic acid is found in the urine after liberal feeding of spinach, and in considerable quantity after the ingestion of a number of drugs including salicylates, antipyrine, amidopyrine, morphine, codeine, barbiturates, chloral, camphor, phenol, and menthol.[7] It is apparent, therefore, that care must be exercised in the interpretation of a positive reduction test, particularly when one of these nonsugar substances may be implicated.

In the ordinary course of digestion, carbohydrates in the diet are absorbed either as pentoses or hexoses. The pentoses are found widely distributed in nature, being present in polysaccharide combination as pentosans in the seeds, roots, stems, and leaves of all forms of plant life. Pentoses are present in the human body, the total content of human organs being estimated at about 10 Gm.[8] Pentoses, although important constituents of nucleic acid and certain intracellular enzymes, are not found in the body in a free state, however, except in the condition of pentosuria.

In considering melituria in children, pentosuria of the alimentary type must be borne in mind, for diets after 6 months of age are apt to contain large amounts of food rich in pentose such as prunes, plums, grapes, cherries, strawberries, blackberries, apples, and other fruits. Ingestion pentosuria is a temporary manifestation disappearing when pentose intake is limited. Johnstone[9] found that seventeen out of eighteen individuals who drank 1½ L. of apple juice were temporarily pentosuric. Joslin[1] likewise indicates that the ingestion of pentose-containing foods in large quantities prompts pentose excretion. In the case being reported, pentosuria occurred after servings moderate in quantity and probably not exceeding the usual assimilation limit as pentose was not present in urine of the two siblings on a similar diet. Glucose is actively and selectively reabsorbed in the proximal convoluted tubules, and hence does not ordinarily pass unhindered into the urine, while the threshold value for pentose is low. Considering the fact that our patient had an associated low threshold for glucose, it was not too difficult to assume that the threshold for pentose was likewise lowered. Pentosuria could, thus, conceivably occur on servings of a size not ordinarily causing a significant alimentary pentosuria.

When the concentration of pentoses in the urine is constant, unaltered by changes in the diet, and influenced only by the administration of drugs, a condition of chronic essential pentosuria exists. Essential pentosuria is considered as an inborn error of metabolism along with albinism, alkaptonuria, cystinuria, and porphyrinuria. The incidence is rare and has been estimated as occurring in one out of 50,000 people.[10] Essential pentosuria is predominantly found in Jewish males and is believed to be inherited as a simple recessive characteristic. The disturbance is generally considered an innocuous asymptomatic metabolic anomaly, although associated symptoms of migraine and manifestations of the so-called vagotonic constitution have been described.[11] Experimentally it has been shown that young rats given a diet containing 35 per cent xylose developed cataracts in approximately the same time as litter mates receiving a diet containing 35 per cent galactose.[12] There have been clinical instances of cataracts reported in galactosuria[13, 14] but none noted in pentosuria.

Pentosuria with diabetic symptoms has been described in an infant 22 months of age presenting a picture of polyphagia, polydipsia, polyuria, and pollakiuria.[15] Levy's case[16] also suggested diabetes in view of a history of weight loss, pallor, and a large output of urine. Essential pentosuria may not only be confused with diabetes mellitus, but may actually occur with it. Voit[17] found a pentosazon in the urine of twelve of fourteen patients with diabetes. A similar concomitance has been noted by other observers.[18-20] Joslin and associates[1] were able to find only one questionable instance of such an association. The concomitance is apparently coincidental for pentosuria and is not related to a disturbed glucose metabolism or to variations in dietary carbohydrate. In most cases of diabetes the metabolism of xylose is likewise normal.[21]

While diabetes and pentosuria are etiologically distinct, their occasional clinical concomitance emphasizes the importance of not only identifying urinary constituents but of ascertaining the circumstances of that excretion. Failure to

recognize both when existing together is dangerous. Insulin dosage based on the urinary sugar is misleading, pentose being excreted constantly and independently of insulin and the blood glucose level. In a diabetic subject a confusing picture of melituria in the face of a normal blood sugar and clinical control, should, therefore, suggest the presence of pentosuria or an associated renal glycosuria.

Renal glycosuria is the usual diagnosis preceding the identification of pentosuria. Lasker and Enklewitz[22] described pentosuria occurring in twins, a case previously mistaken for juvenile diabetes mellitus and later for renal glycosuria. Both renal glycosuria and pentosuria are asymptomatic disease entities, often familial, benign in their course, and showing no tendency to progress toward diabetes. Both yield normal fasting blood sugar values, glucose, and pentose tolerance curves. Renal diabetes is associated with the excretion of a fermentable hexose. The renal function as a whole is normal,[23-25] though tubular reabsorption of glucose is diminished. Pentosuria, on the other hand, is associated with the excretion of a nonfermentable 5 carbon monosaccharide. Pentosuria is ascribed to an abnormal enzyme system which decarboxylates glycuronic acid and converts it into xyloketose. A fermentation test should be of value in helping to identify the two meliturias as independent entities, but certainly not when they occur together. Recorded instances[26, 27] of renal glycosuria associated with pentosuria are accordingly infrequently reported, probably due to the fact that a possibility of a combination of excreted sugars is not considered too often.

In the case being reported, a combination of sugars was suggested by conflicting fermentation reports. Negative fermentation studies on urines obtained shortly after breakfast and yielding a positive qualitative Benedict's test (0.3 to 0.4 per cent quantitative) were reported on several occasions, while late afternoon specimens fermented strongly. The observation that postcibal morning specimens contained a nonfermentable reducing substance not obscured by a fermentable reducing component occurring later in the day suggested that the former was probably contained in quantity in the breakfast meal. Pentosuria seemed likely in view of the regularity of ingestion of moderate quantities of pentose containing foods. Lactose and galactose, also nonfermentable sugars, were excluded on the basis of the tests outlined. Bial's modification of the orcin test was positive for pentose. The pholoroglucinol test was confirmatory for a pentose. With the phenylhydrazine test, crystalline osazones precipitated out in a yellow, flaky mass composed of long, yellow, needle-shaped crystals characteristic of pentasazons. Their appearance was identical with that of the osazones obtained from a known sample of pentose. The oral glucose tolerance curve excluded diabetes mellitus, suspected because of the diabetic symptomatology. The collected urines demonstrated a low renal threshold for glucose. The intravenous glucose tolerance test, apparently applicable to infants and children[3] ruled out hepatic disease, as did the other liver function tests indicated. Intravenous pyelograms and normal values for nonprotein nitrogen, urea nitrogen, and creatinine indicated good kidney function. The pentose tolerance curve was similar to that seen in nor-

tion. The stained tibias were rated in terms of decalcification of the metaphyses, in contrast to the therapeutic experiments where degrees of recalcification were used for interpretation. The roentgenographs demonstrate the condition of the animals during the course of the experimental period, but the magnified microphotographs show more clearly than the x-rays the difference between the prophylactic effect of the three methods. The initial readings for metaphyseal width in the weanling rats, averaging approximately one, do not express the degree of rickets but rather indicate the normal cartilagenous character of the undeveloped infantile bones. During normal development this cartilaginous zone diminishes as calcification proceeds.

All three methods of administering single massive doses of vitamin D proved to have a prolonged protective effect. At the end of the first month the metaphyseal widths decreased normally in all groups. In the groups receiving the parenteral doses the bones continued to calcify normally throughout the entire three-month period. However, in the group receiving oral doses in oil, no further decrease but rather a slight, progressive increase in the average width of the metaphyses was observed after the second and third month. The incidence of this decalcification, though quantitatively small, was sufficient to give it significance.

A statistical analysis of the data derived from the microphotographs is presented in Table V. It shows that after one month the width of the metaphyses diminished to about the same degree in all groups. After two and three months, however, differences became apparent. The prophylactic effect of parenterally administered vitamin D doses proved to be superior to that of oral doses. The statistical significance of these differences is expressed by t-values of 3.3 and 3.7 after two months, and of 2.1 and 2.6 after three months, when the animals receiving vitamin D in oil by mouth were compared with the groups receiving parenteral vitamin D doses in oil and in oil-ether solution.

TABLE V. SUMMARY OF STATISTICAL DATA FOR PROPHYLACTIC TESTS

GROUP	METHOD OF DOSAGE*	DURATION OF TEST (DAYS)	RATINGS OF METAPHYSIS WIDTHS		SIGNIFICANCE OF DIFFERENCE†	
			AVERAGE	STANDARD ERROR	GROUPS COMPARED	T-VALUE
J	OO	30	0.60	±0.120	J and M	1.2
M	IMO	30	0.40	±0.106	M and P	1.0
P	IMOE	30	0.56	±0.111	P and J	0.2
K	OO	60	0.82	±0.217	K and N	3.3
N	IMO	60	0.07	±0.034	N and Q	1.4
Q	IMOE	60	0.02	±0.013	Q and K	3.7
L	OO	90	0.73	±0.280	L and O	2.1
O	IMO	90	0.10	±0.10	O and R	1.0
R	IMOE	90	0.0	±0.0	R and L	2.6

*OO, oral, in oil medium; IMO, intramuscular in oil medium; IMOE, intramuscular in oil-ether medium.

†For groups of this size a t-value of 2.1 indicates a significant difference.

SUMMARY AND CONCLUSIONS

Experiments on rats were carried out to determine the comparative therapeutic and prophylactic effect of a single massive dose of vitamin D_2 administered orally in oil, intramuscularly in oil, and intramuscularly in oil-ether solution. All animals were followed by x-ray, and examined by the line test. The line test data were submitted to statistical analysis.

Six days following the administration of 1,000 units of vitamin D_2 to rachitic rats, the average degree of line test healing was 3.32 with the intramuscular oil-ether injection, 3.13 with the oral administration in oil, but only 2.57 with the intramuscular injection in oil. The superiority of the oil-ether injection and the oral dose over the parenteral administration in oily solution was statistically significant.

The protective effect of a single dose of 1,000 units of vitamin D_2 showed differences between the three methods only after two and three months. Three months following the administration of the prophylactic doses, the average degree of decalcification was 0.0 with the oil-ether injection, 0.1 with the oil injection, and 0.72 with the oral doses in oil. The superiority of the oil-ether injection and the oil injection over the oral doses was statistically significant.

The superiority of the parenteral vitamin D_2 administration in an oil-ether vehicle in the therapeutic as well as the prophylactic experiments seems to indicate quick absorption and satisfactory retention of the vitamin administered by this method.

The inferiority of the parenteral administration of vitamin D_2 in oil in the therapeutic experiments may be ascribed to a delayed vitamin D absorption from the oily deposit in the tissues.

The inferiority of the oral administration of vitamin D_2 in oil in the prophylactic experiments may be explained by incomplete absorption of massive doses from the gastrointestinal tract and loss of vitamin D with the feces.

If observations in animals are applicable to infants and children, one may expect that intramuscular injection of a single massive dose of vitamin D_2 in an oil-ether vehicle cures rickets at least as promptly as other methods of administration, and is at least equivalent to the other methods in its prophylactic effect, giving complete protection against rickets for at least three months. Impressions gained from clinical experience[2] are in conformity with these deductions.

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CAPILLARY FRAGILITY AND MENSES IN RHEUMATIC GIRLS

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THIS paper discusses the duration and frequency of menses in twenty-eight ambulant rheumatic girls, and records capillary resistance in various phases of their menstrual cycle. We are unable to locate a similar study.

Capillary resistance was determined with a modified Dalldorf resistometer, as previously described.[1] Capillary resistance is the minimal amount of suction (centimeters of mercury negative pressure) applied for one minute to the skin of the forearm just below the antecubital space, which produces one petechia or more. Normal values are dependent on many factors, including season and age. At age 13.4 years, the average for this group, capillary resistance in non-rheumatic children is about 27 cm., and in rheumatic children, 17.4 cm.[1, 2] When values of 10 cm. are obtained, capillary resistance is distinctly abnormal, and at 5 cm., capillary fragility is extreme.

Several diseases produce capillary fragility and excessive menstrual flow, sometimes hastening the appearance of menses. In scarlet fever, streptococcus toxin causes low capillary resistance[1, 3] and menorrhagia.[4] Measles is attended with extreme capillary fragility[5] and menses in the presence of an attack may occur early and be more severe.[4] Pneumonia produces low capillary resistance[6] and at times an excessive menstrual flow.[7] If infection develops immediately after menstruation, recurrence of the bleeding may occasionally occur.[4]

In rheumatic patients there is evidence of increased capillary permeability[2, 8, 9] and hemorrhagic phenomena.[9]

In normal subjects the age of menarche, duration of menses, and length of menstrual cycle may be quite variable. The peak age of menarche is observed at 13 years.[10, 11, 13, 14] In one series of 10,000 cases it was 13.9 years.[15] Puberty tends to be delayed in northern Europe (Scandinavia) while in Italy and Greece it may commence as early as ages 10 to 12.[16]

The duration of menses is usually three to five days,[12, 17] but both lesser and greater periods of menstrual flow occur in healthy girls. The length of the menstrual cycle was determined by Arey[18] in about 1,500 women and girls, including some 20,000 calendar records. The commonest length of 8,462 cycles (furnished by 585 persons) is twenty-eight days both for puberal girls and for adult women. The average length of all cycles is 33.9 days for girls and 29.5 days for women.

In this study, to determine variations in capillary resistance, the menstrual cycle was divided into three stages: (1) premenstrual, from the fourth day preceding menses to and including the first and second day of menses, (2)

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menstrual, from the third day to the end of menses and (3) intermenstrual, from the end of menses to the fourth day prior to next menses. The premenstrual stage arbitrarily included the first two days of menses since it has been shown that capillary resistance in normal healthy female subjects is lowest during the few days prior to and on the first and second days of menstruation.[19, 20] Capillary resistance readings in twenty-eight rheumatic girls may be noted in Table I.

TABLE I. MENSTRUAL DATA IN TWENTY-EIGHT RHEUMATIC GIRLS

PATIENT	AGE	AGE AT MENARCHE	DURATION OF MENSES (DAYS)	MENSTRUAL CYCLE (DAYS)	CAPILLARY RESISTANCE (CM. OF HG SUCTION)					
					PREMENSTRUAL*	AVERAGE	MENSTRUAL*	AVERAGE	INTERMENSTRUAL	AVERAGE
S. C.	15		5-6	21-28		20		20	(15,25)	20
V. W.	15	13	3-5	24-30	(15,25)	20		25	(15,15)	15
N. D.	13	13	5	28		15		—	(20,30)	25
H. T.	13	12	6-7	28-42		5		10		20
N. B.	13	12	6-7	28		—		—	(15,15)	15
J. G.	13	11½	4-5	21-30		—		15	(15,20)	17½
Y. W.	14	—	4-6	30		20		—		15
K. S.	11	11	4-5	—		15		10		25
H. W.	15	—	5-6	21-28	(25,10)	17½		10		15
E. F.	14	—	4	—		—		—		15
C. M.	16	13	4	26-28		10		—		10
B. W.	14	14	7	28	(10,10)	10		—	(20,15,10)	15
R. G.	11	10½	3-7	21-28		—		—		15
B. I.	13	12	4	28		—		15		15
L. L.	14	—	4-14	28		—		10		15
V. M.	14	—	5	—		15		25	(20,25,15)	20
T. M.	13	—	5-8	21		10		15		20
R. D.	13	12½	5	26-28		15		—		20
L. S.	12	12	5	—		—		—		15
M. P.	13	12	3-4	28		25		—		25
I. J.	13	—	5	—		—		—	(15,15)	15
L. C.	14	—	3-7	14-28		10		—	(10,15,20)	15
V. G.	12	10	3-4	30		—	(20,15)	17½	(15,20)	17½
R. D.	11	11	4-6	28		5	(5,5)	5	(5,5,15)	8
F. A.	16	—	4-5	—		10		—		20
E. G.	11	10	5	28-30		—		—	(20,15,5)	13
E. P.	15	13	4	26		—		—	(10,20)	15
A. A.	15	—	4-7	21-28	(10,10)	10		10	(5,15,15)	12
Average	13.4	11.9	5.1	26.9		13.7		14.4		16.7

*As defined in text.

SUMMARY AND DISCUSSION

Age of Menarche.—The onset of menses tended to be early in this group of rheumatic girls, records being available in only seventeen cases. Three girls started to menstruate at age 10. The average age of menarche was 11.9 years, in contrast to 13½ years, the average age for American girls.[14]

Length of Menses.—This averaged 5.1 days in twenty-eight rheumatic girls, several having periods lasting seven days or longer. In nonrheumatic girls, the average duration is closer to four days.

Menstrual Cycle.—The interval between menstrual periods averaged 26.9 days, as compared with 33.9 days for nonrheumatic girls.[18]

Capillary Resistance.—The average capillary resistance during the four days prior to menses and the first two days of menses was 13.9 cm. It rose

slightly to 14.4 cm. during the remainder of menses. In the intermenstrual period capillary resistance was 16.7 cm., a rise of 3.0 cm. over the premenstrual phase. It is generally accepted that some glandular influence, probably ovarian, is responsible for lowered capillary resistance and general tissue congestion in the premenstrual phase. However, this glandular influence on capillary resistance is not so great as that produced by a seasonal influence, which is worthy of comment.

The seasonal influence on capillary resistance was noted by Roberts and her co-workers[21] in eighty-five institution children. These workers found that capillary resistance was 23 cm. in August and 16.5 cm. in April. In rheumatic children we[2] noted an even greater seasonal variation, capillary resistance being 23.3 cm. in September and 14.2 cm. in February and March, a difference of 9.1 cm. We stated our belief that streptococcus toxin may be important in accounting for these seasonal variations.[1, 2]

It was formerly held that vitamin C deficiency might explain seasonal variations in capillary resistance noted in large groups. Two factors, however, rule out the influence of this vitamin. The first is the failure of thirteen groups of workers either to improve capillary resistance by administering vitamin C or to find any definite relationship between blood ascorbic acid values and capillary resistance.[1] The second weakness in the vitamin theory is that it does not explain the sudden drop in capillary resistance noted in the fall.[1, 21]

The sudden increase in capillary fragility noted in the fall is probably caused by increased amounts of streptococcal toxins in the blood following the first chilling weather.[1]

Seasonal variation in capillary resistance may be the effect of streptococcal toxin in both rheumatic and nonrheumatic individuals. The streptococcus is uniformly present in all pharynges.[1] Streptococcic activity is minimal at the end of summer and capillary resistance is highest at this time.. Following the first chilling weather in the fall, there is a mass onset of streptococcic colds,[22] and many symptoms appear which might be caused by the streptococcus such as sniffing, hacking, muscular aches, sinusitis, and rheumatic fever. There is a coincidental sudden drop in capillary resistance. However, the peak of streptococcic and rheumatic activity is reached in the spring when capillary resistance is lowest.

In summary, then, it may be stated that while the glandular influence on capillary resistance seen in the menstrual cycle is considerable (3.0 cm.), it is of lesser magnitude than the influence of various infections, such as streptococcus infections, rheumatic fever, scarlet fever, pneumonia, and measles. These infections not only lower capillary resistance greatly but may precipitate menses and produce menorrhagia.[4, 7, 23]

CONCLUSIONS

1. Bleeding phenomena in rheumatic girls are evidenced by an early menarche, prolongation of menses and shortening of the menstrual cycle.

2. The bleeding tendency is increased during the premenstrual and menstrual phase, at which time there is a diminished capillary resistance amounting

to 3 cm. of mercury suction. This capillary fragility is presumably under glandular control.

3. An even greater influence in producing the capillary fragility and menorrhagia of rheumatic girls is exerted by rheumatic toxin.

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Case Reports

MENINGITIS DUE TO SALMONELLA MANHATTAN

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MENINGITIS caused by a Salmonella organism has been reported in ninety-three instances. The mortality rate in the reported cases has been high. Among the drugs used, sulfonamides have been the most effective. Sulfaguanidine is effective against *Salmonella paratyphi A* and *Salmonella choleraesuis* but ineffective against other organisms of the Salmonella group.[1] Sulfanilamide, sulfathiazole, and sulfadiazine have been used.

The following report is of a one-month-old infant who had enteritis and meningitis caused by *Salmonella manhattan* and who recovered following the use of streptomycin.

This female infant was seen July 6, 1946. At that time a history of having had a slight persistent diarrhea since the fourth day following delivery was noted. She was sent home from the hospital nursery on the eighth day of life. She was breast fed with a complementary evaporated milk formula. The infant was irritable, and had diarrhea. At the age of 17 days, a physician changed the formula to homogenized milk, but the diarrhea persisted. It was not until two days prior to admission to Milwaukee Children's Hospital at the age of one month that the diarrhea became severe, and the infant passed ten to twelve green, watery stools daily.

The past history was as follows: the health of the mother during her prenatal period was excellent; Wassermann test was negative; and delivery was made by low forceps. Although alleged to be three weeks premature, the child weighed 6 pounds, 8 ounces at birth and was perfectly healthy. She was the fifth sibling. The family history was essentially negative for important hereditary diseases and also negative for infectious diseases during the mother's prenatal period.

Physical examination on admission to Milwaukee Children's Hospital revealed a critically ill female infant one month of age, with a subnormal temperature and a tense anterior fontanel. Nystagmus was present and the child was slightly hypertonic. The pharynx was mildly injected. A spinal puncture was performed immediately. The fluid obtained was under moderately increased pressure, turbid, and opalescent. Further examination revealed 3,080 cells per cubic centimeter, a 4 plus Pandy, and 9 mg. per cent sugar. A gram-negative organism was found and tentatively identified by smear as *Hemophilus influenzae*. Immediate therapy consisted of intravenous 5 per cent glucose in normal saline to restore hydration and 22.5 grains of subcutaneous sulfadiazine. This initial amount was followed by 3.3 grains every four hours (approximately 2½ to 3 grains per pound of body weight daily). Because of the tentative identification of the organism as *H. influenzae type B*, 100 mg. of Alexander's anti-influenzal serum was given intravenously. No further serum therapy was given because the laboratory later identified the organism by culture as not *H. influenzae type B*, but as *Bacillus paratyphosus*. Because of the conflicting

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laboratory reports, the organism was sent to Dr. P. R. Edwards of the National Salmonella Center, Agricultural Experiment Station, Lexington, Ky.[2] Doctor Edwards identified the organism as *S. manhattan* (V1, V111, d, 1, 5). The identifying characteristics of this motile, gram-negative organism were as follows: lactose, negative; saccharose, negative; dextrin, negative; dextrose, acid and gas; mannite, acid and gas; maltose, acid and gas; xylose, acid and gas; dulcitol, acid and gas; salicin, negative; sucrose, negative; H_2S, positive; indol, negative; gelatin, not liquefied; lead acetate, blackened in eighteen hours; litmus milk, acid.

Streptomycin was given intramuscularly, 25,000 μg per pound body weight daily in divided doses every three hours, and intrathecally 25,000 micrograms once daily, as recommended by Dr. Chester Keefer of the National Research Council, Committee on Chemotherapeutics. Sulfadiazine therapy was continued until the organism was identified temporarily as one of the Salmonella group (fifth hospital day). The amount of sulfadiazine given was approximately 2.5 grains per pound body weight daily. During these five days of hospitalization the patient continued to become more spastic and developed difficulty in swallowing. At the time sulfadiazine was discontinued, the cultures of both the stool and spinal fluid showed the pathogen still present (Table I). The child was

TABLE I. SUMMARY OF SPINAL AND CISTERNAL FLUID FINDINGS

DATE	7/6	7/8	7/9	7/15	7/16	7/19	7/24	8/9	8/23
No. cells	3,080	3,480	1,300	65	109	177	212	26	12
Sugar (mg. %)	9	25	29	33	49	32	33	48	47
Culture	pos.	—	pos.	neg.	—	neg.	neg.	—	—
Pandy	+++	++	+++	++	++	++	++	+	tr.

having momentary twitchings and convulsions, and the spinal fluid was becoming more difficult to obtain from the lumbar level. Heparin was not given intrathecally as advised by Alexander,[3] but small amounts of air were injected intrathecally in the hope that a complete block would not occur. A block, however, did occur, and cisternal taps had to be resorted to for the intrathecal injections of the streptomycin. The condition of the child on the sixth day was very poor. She was convulsing continuously, even with phenobarbital sedation.

On the tenth hospital day, 60 c.c. of blood were given intravenously and it was noted that from that day on the fever became of a low-grade type.

On the tenth day of streptomycin therapy, a rash was noted, particularly over both lower extremities and on the chest. Most of the lesions were erythematous, some were of the roseolar type, and some were persistent, large wheals of the angioneurotic edema type. There was marked dermographism. This eruption rapidly disappeared on cessation of streptomycin administration on the fourteenth hospital day. The dermographism, however, persisted for a longer time. The rash was considered to be due to a streptomycin toxic manifestation rather than one produced by meningitis.

The spinal fluid became negative for organisms on the sixth hospital day (four days after streptomycin was begun), and the stool cultures were negative on the fourteenth day. The spinal fluid was again obtained by lumbar puncture on the thirty-fifth hospital day, and it was assumed that the spinal fluid block was released spontaneously. Blood culture was never positive for organisms. It is regrettable that a blood culture was not taken until after the spinal fluid became negative. At no time was a posiitve agglutination reaction obtained with the child's serum, as expected, because a child this age does not readily manufacture antibodies. On discharge (the fiftieth hospital day) the child appeared in good general health (having gained one pound, 14 ounces since admission):

the neck was not stiff; the pupils were equal and reacted to light; no ptosis or nystagmus was present; and there was no facial palsy. Two weeks after discharge the child was rechecked in the clinic and at that time no abnormal neurologic findings were present.

In the hope of ascertaining the source of the infection, epidemiologic studies were begun by the Milwaukee City Health Department. All contacts of the child in the home and in the hospital where the child was born were examined. This included father, mother, grandparents, doctors, nurses, and nursery aides. Urine and stool cultures were obtained from everyone known to have been or suspected of having been in contact with the child or its food. Blood agglutinations were done on the immediate family. No evidence of carriers was found.

SUMMARY

1. The case of a patient with *S. manhattan* meningitis is reported. This is the first case of *S. manhattan* meningitis reported in the literature.

2. Recovery without sequelae followed treatment of the case with streptomycin.

3. Because of a block of the spinal fluid, the cisternal route of administration had to be used.

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HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

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IT IS well established that among adults the condition known as hypertrophic pulmonary osteoarthropathy (Pierre-Marie-Bamberger's Disease), found in long-standing pulmonary or cardiac disease, is not uncommon. However, most authorities agree that the condition is rare in children. Caffey[3] states that in twenty years at Babies' Hospital no cases have come to his attention. That the condition does occur more often in children than is suspected is noted by Kennedy, who describes a case in a 7½-month-old infant with multiple lung abscesses and bronchopneumonia.

A few instances of this condition and its rarity have also been noted by others. E. Miller[16] reports a case of a 14-year-old boy with reticulum cell sarcoma of the thymus. Kline reports another case in a 14-year-old boy with tuberculosis of the knee, spine, and lungs. D. M. J. Miller[15] reports still another case in an 8-year-old child with pneumonia and purulent bronchitis. He also quotes Whitman, Davis, Thorbum, and Gillet as having seen cases of hypertrophic pulmonary osteoarthropathy in children.

ETIOLOGY

The underlying causes are many, but the primary precipitating etiologic agent of this condition is still unknown. Hypertrophic pulmonary osteoarthropathy, as the name implies, is most often associated with, and secondary to chronic pulmonary infections, usually lung abscess, bronchiectasis, bronchial asthma of long standing, chronic bronchitis, and late carcinoma of the lung. Pulmonary tuberculosis is one of the few chronic conditions of the lung in which this bony alteration is very infrequently found. However, Kessel[11] reports that among 100 patients with advanced pulmonary tuberculosis there were some manifestations of hypertrophic pulmonary osteoarthropathy in certain cases.

The second underlying cause is chronic heart disease, especially the congenital type. The condition is also ascribed to other causes of lesser importance, i.e., chronic diseases of the liver and intestinal tract, polycythemia vera, hypothyroidism, thymic tumors, and other mediastinal growths. Dyspituitarism has also been considered one of the causes.

Hypertrophic pulmonary osteoarthropathy of idiopathic type and unknown etiology in families has also been described by Freund,[5] Campbell, and Sacosa.[4]

In reference to the primary etiologic agent for this disease, Mendlowitz and Leslie[14] have been able to preproduce this pathologic entity experimentally in a dog by the anastomosis of the left auricle to the left pulmonary artery. This resulted in an increase of cardiac output. It was concluded that the bony changes produced may have been due to the constantly excessive peripheral blood volume increasing periosteal nutrition and thus stimulating bone proliferation.

Other investigators, such as Funk[7] and Kessel,[11] ascribe the alterations of the periosteum to toxins or venous stasis.

PATHOLOGY AND CLINICAL FINDINGS

The cortical bone may become thin while the periosteal tissue will thicken occasionally to as much as 6 to 8 mm. Eventually hyalinization will take place

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and finally ossification of the periosteum, whose external surface may merge with the skeletal muscle. This ossified periosteum, having an irregular contour, may become indistinguishable from the underlying cortical bone.

The rapidity of development of these bony changes varies considerably. In some cases, periostitis develops within a few months after the initial pulmonary disease. In others, the bony alterations may not develop until many years. The changes usually involve the distal thirds of the long bones, and may affect the ulna, radius, tibia, and fibula. To a lesser extent the humerus, femur, carpals, metacarpals, and proximal phalanges may be involved. The process later extends proximally, and may involve the entire bone.

The early joint changes are confined largely to the periarticular tissues. In the later stages, erosion of the cartilage, lipping at the articular edges, and even a moderate degree of ankylosis may develop. Pain may accompany the periostitis and these arthritic changes.

Clubbing of the fingers and/or toes is always found associated with hypertrophic pulmonary osteoarthropathy; it merely represents the first stage in this disease. The phenomenon of clubbing is due to soft tissue swelling and usually is not associated with thickening of the terminal tufts or overlying periostitis.

Both the periostitis and the clubbing may diminish in severity and become less marked in proportion to the improvement of the suppurative pulmonary condition. They may even disappear entirely, only to recur with the exacerbation of the pulmonary disease. However, the condition is not always a reversible one, and the bony changes may remain permanently, even though the patient may be clinically cured.

Some authors report peculiar facial alterations associated with this condition. This consists of a thickening of the subcutaneous tissues about the nose and malar prominences, so that the nose and facies assume a globular appearance. Prognanthism may be observed, but it is not as marked as in acromegaly.

CASE HISTORY

The patient is a 2-year-old white female, admitted to New York City Hospital on April 1, 1946. Her chief symptoms were chronic cough of four months' duration, considerable weight loss, and anorexia. The cough was not productive.

Present Illness.—Since January, 1946, when the patient developed a "cold" not responding to therapy, she was ill with cough, dyspnea, and loss of about 15 lbs. The child had a normal birth; her diet was adequate. Five older siblings are all living and well. The mother is in good health; the father died, cause unknown. There have been no previous illnesses and no familial history of tuberculosis or any other contact infection.

Physical Examination.—The patient appeared chronically ill and emaciated, with drawn facies. Temperature was 99° F.; pulse, 120 per minute; respiration rate, 40 per minute.

Findings were essentially negative except as noted below.

Head and Neck.—Moderate posterior cervical adenopathy, not tender.

Chest.—Movements were restricted during respiration, especially on the right side.

Heart was normal, except for tachycardia.

Lungs showed tactile fremitus, diminished on the right side anteriorly and posteriorly, and there was dullness to percussion in the same regions. The breath sounds were tubular in quality and bronchophony was present over the upper third of the right chest. Breath sounds were diminished over the lower half of right chest, posteriorly. There were coarse moist râles scattered throughout both left and right sides, posteriorly.

Extremities.—Marked clubbing of the distal ends of all fingers and toes was present.

Course.—On the day of admission a roentgenogram of the chest (Fig. 1) showed that the right lung was collapsed and a hydropneumothorax was present, the fluid level being at the fourth interspace anteriorly. A thoracentesis was performed the following day, but only a few drops of turbid, blood-tinged material were obtained. Smear of this fluid showed a considerable number of pus cells, but was negative for any bacterial pathogens. The patient was given multiple small blood transfusions and placed on penicillin therapy (20,000 units every three hours). Temperature course was very irregular, at times reaching 101° F., and the patient showed no significant response to penicillin therapy. This therapy was given in long repeated courses throughout the period of illness. On April 29 the patient's cough became productive of a small amount of cream-colored sputum. Repeated roentgenograms of the chest showed slight diminution in the amount of fluid at the right base. Otherwise, the findings were unchanged.

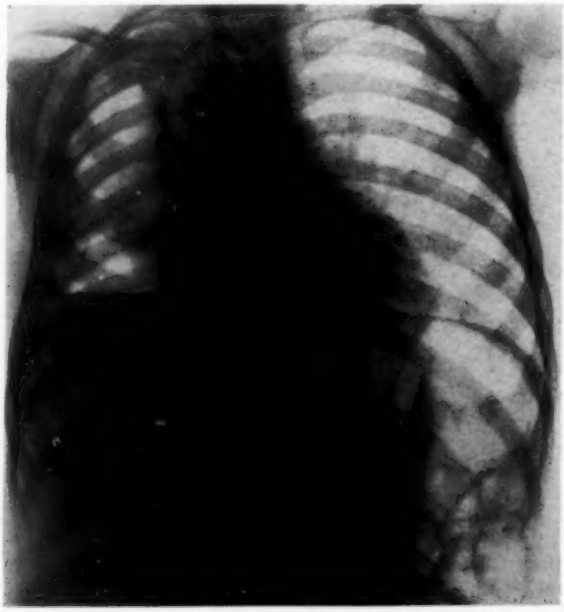

Fig. 1.—Roentgenogram of chest on day of admission shows collapse of the right lung and fluid level at fourth anterior interspace. Heart and mediastinal contents are displaced slightly to the right.

Bronchoscopy on May 2 showed a large amount of mucopurulent material present in the right main bronchus. The pus had no foul odor. A bronchogram showed no evidence of bronchopleural fistula at this time.

On June 7 a thoracotomy was performed by partial resection of the eighth rib. Considerable pus was drained and thereafter the child began to show slow but definite clinical improvement. The temperature still rose to 101° F. at times. Clubbing of fingers persisted in the same severity. Roentgenogram of long bones taken July 3, 1946, showed considerable thickening and periosteal proliferation in the femur, tibia and fibula, radius, and ulna bilaterally, including the distal half of both humeri. Repeated radiographic study of long

bones on July 25 showed no change in this periosteal proliferation (Figs. 2 and 3). A diagnosis of hypertrophic pulmonary osteoarthropathy was made secondary to the chronic empyema.

The subsequent course of illness was essentially unchanged, except for development of a bronchopleural fistula. On September 5, temperature rose to 104° F. and did not fall. More extensive rib resection was performed by partial removal of the fifth to ninth ribs on the right side. Very little drainage was obtained. The temperature fell somewhat, and the child showed some clinical improvement. Roentgenogram of the chest at this time showed slight re-expansion of the right upper lobe; less fluid was present at the right base than on previous examination. Otherwise, findings were essentially unchanged.

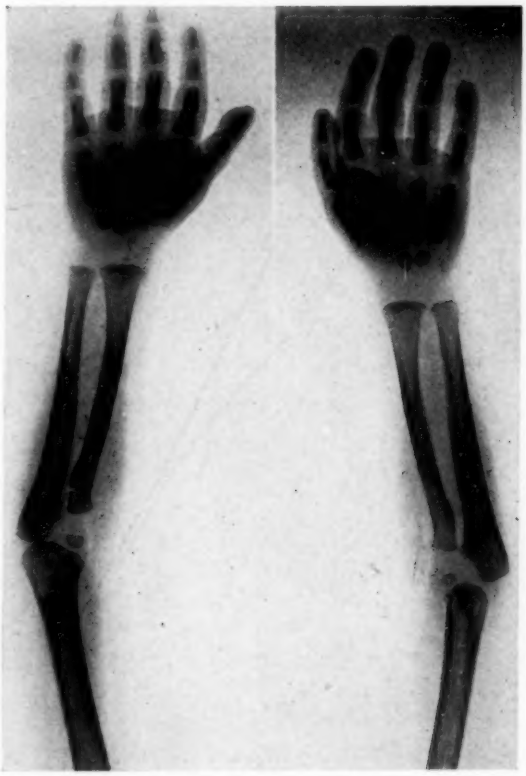

Fig. 2.—Roentgenogram of the upper extremities taken July 3, 1946, shows marked thickening and proliferation of the periosteum along the shafts of the radius, ulna, and distal half of the humerus, bilaterally.

Blood counts during the course of the disease showed a relative and absolute lymphocytosis. This was attributed to the chronicity of the illness.

Bone marrow puncture performed Sept. 15, 1946, showed a relatively high proportion of cells of the lymphocytic series in the mature stage, with a tendency toward hypoplasia of both the myeloid and lymphocytic series. These findings were not consistent with that of the lymphoblastomas or leucemia.

Repeated smears and cultures throughout the course of the illness taken from sputa, bronchoscopy, and from several thoracotomy procedures were negative for tubercle bacilli. Guinea pig inoculations were also negative. At times cryptococci were found in some cultures; *Staphylococcus aureus* and Gram-positive rods and *Bacillus pyocyaneus* were also found. On July 8, and throughout the course of the illness after this date nonspecific yeastlike fungi were found. These increased in amount as the illness progressed.

Many courses of penicillin therapy were instituted, including local irrigation into the pleural cavity. Sulfadiazine was also given in adequate doses for some time. However, during all the time described, remissions were only to be followed by exacerbations. The latter were of decreasing severity.

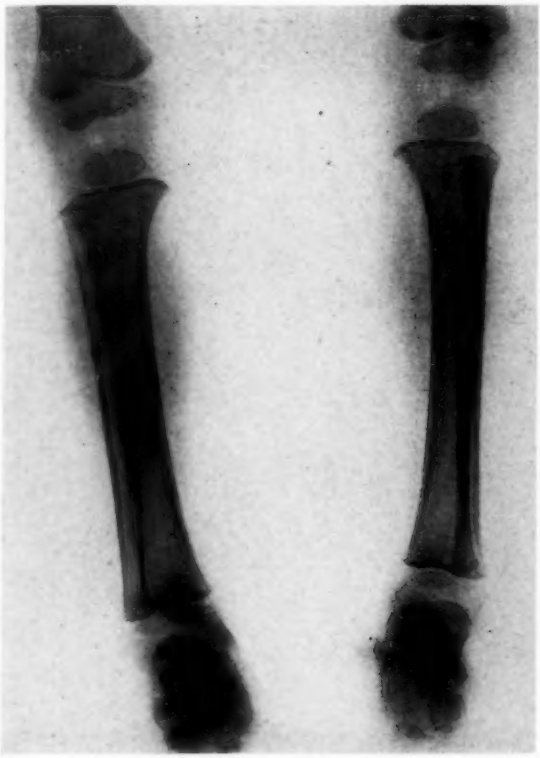

Fig. 3.—Roentgenogram of lower extremities taken July 3, 1946, shows considerable thickening of the periosteum along the shafts of the tibia and fibula, bilaterally.

On October 12, streptomycin therapy was begun, using 25 mg. per kilogram per day.

On October 19, the patient was transferred to Babies' Hospital for special thoracic surgery.

Transfer Diagnosis.—(1) chronic pyopneumothorax, right side, and (2) hypertrophic pulmonary osteoarthropathy was the diagnosis.

Laboratory Data.—Wassermann and Mazzini blood reactions were negative; urinalyses were repeatedly negative.

April 4, 1946, the red blood cells were 3,100,000; hemoglobin, 11.0 Gm.; white blood cells, 8,000; neutrophiles, 40 per cent; lymphocytes, 40 per cent; monocytes, 12 per cent; and lymphoblasts, 8 per cent.

May 11, blood cholesterol was 106 mg. per cent; cholesterol ester, 66 mg. per cent; and albumin globulin ratio, 3.2/4.3.

May 24, the blood culture was negative. Repeated blood cultures on several later occasions were negative.

May 25, the Congo red test was 62 per cent present in serum after one hour.

July 30, red blood cells were 4,700,000; hemoglobin, 11.0 Gm.; white blood cells, 13,250; neutrophiles, 20 per cent; lymphocytes, 76 per cent; eosinophiles, 2 per cent; monocytes, 2 per cent; numerous toxic granulocytes were noted.

September 18, red blood cells were 4,600,000; hemoglobin, 11.0 Gm.; white blood cells, 25,000; neutrophiles, 11 per cent; lymphocytes, 81 per cent; monocytes, 7 per cent; basophiles, 1 per cent; numerous toxic granulocytes were noted.

CONCLUSION

1. The rarity of hypertrophic pulmonary osteoarthropathy in children is noted, together with a brief review of the literature of the condition.

2. A case history is presented of a 2-year-old child having chronic pyopneumothorax, associated with hypertrophic pulmonary osteoarthropathy.

The authors wish to acknowledge their gratitude to the Pediatrics Department, City Hospital, New York, for their cooperation in the production of this paper.

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FATAL SICKLE CELL ANEMIA IN A ONE-MONTH-OLD INFANT

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SINCE Herrick[1] first described the entity of sickle cell anemia in 1910, recurring reports have appeared in the American literature discussing the disease, its appearance, its manifestations, and the outcome. It is not the purpose of this paper to review the disease in its entirety, but rather to emphasize the occasional early onset and to re-emphasize the criteria for diagnosis.

A differentiation must be made between sickle cell anemia with crisis and "sicklemia," the sickling trait without anemia. Sicklemia is characterized only by the appearance of true sickle cells in sealed moist blood preparations without any hematologic evidence of anemia or any constitutional evidence of increased blood destruction. The incidence of sicklemia has been described as occurring in from 5 to 10 per cent of American Negroes.[2] Not more than 10 per cent of such individuals went on to develop the associated anemia Sydenstricker[3] did not encounter an instance of sicklemia in a series of over 1,000 white individuals, and has reported an incidence of the sickling trait in 7 per cent of 1,000 negroes examined. In the outpatient department of Babies' Hospital[4] the blood of 150 Negro patients was examined, and thirteen or 8.6 per cent showed latent sickling, while the blood of white children did not show this phenomenon. Cooley[5] found 7.5 per cent incidence of sicklemia among Negroes in Detroit. Despite the failure to demonstrate the occurrence of the sickling trait in pure white persons when mass surveys were conducted, isolated cases of sickle cell anemia in patients of undoubted white heritage have been reported from time to time.[6-8] Elliptocytosis of the red blood cells, with and without an associated anemia, has been described as occurring with a familial incidence in white people. This must be differentiated from the true sicklemia and sickle cell anemia. The condition was originally described by Dresbach in 1904, and lately has been extensively reviewed by Lambrecht,[9] Wyandt and associates,[10] and by Huck.[11]

Sickling has been reported at all ages, and in the neonatal period.[2] Mulherin[12] examined the peripheral and cord blood of two infants whose mothers were suffering from sickle cell anemia, and found typical sickle cells. The peak incidence is during childhood, with a sharp decline following adolescence. There have been some cases reported during infancy, the youngest of which was reported by Wollstein and Kreidel[4] at 3 months of age. Branch[13] reported a case in a 6-month-old infant. Experience has shown that the earlier the onset occurs, the more severe is the disease and the poorer is the ultimate prognosis. While intercurrent infection is the most common cause of death in young children with the disease, Wollstein[4] feels that, in some fulminating cases, death may be caused by the anemia, per se.

The criteria for the diagnosis of sickle cell anemia are those for the diagnosis of any acute and chronic hemolytic anemia with the addition of demonstrable sickling of the erythrocytes, more commonly in incubated wet preparations and occasionally, where the disease is severe, in the stained blood film. Other causes for hemolysis should be excluded. It is a heredofamilial disease transmitted as a Mendelian dominant, subject to crisis and spontaneous remissions. The diagnosis of sicklemia may be established by demonstration of the

From the Pediatric Service of Dr. Harry S. Altman.

typically misshapen erythrocytes in wet blood preparations after twenty-four hours, and by the confirmatory differential sedimentation rates of oxygenated and carbon-dioxide saturated specimens of venous blood as described by Winsor and Burch.[14]

A case of sickle cell anemia in crisis with fatal termination in a one-month-old female Puerto Rican infant is presented.

J. C., a one-month-old Puerto Rican girl, was admitted to the Pediatric Service of Lincoln Hospital for fever and incessant crying of one day's duration. She had been a premature baby with a birth weight of 5 pounds and 2 ounces. Following an uneventful ten-day neonatal course in the premature nursery of this hospital, during which she had gained 8½ oz., she had been discharged home. On readmission her weight was 6 pounds and 12 ounces. On physical examination a red and moderately bulging left eardrum was seen. Temperature was 102.4° F. The leucocytes numbered 13,200 per mm.^{3} with 66 per cent polymorphonuclears and 34 per cent lymphocytes. Hemoglobin was 11.5 Gm. per 100 c.c. by the Sahli method. Urinalysis showed two to three erythrocytes and one to two leucocytes per high power field of a voided specimen. The urine was negative for albumin, glucose, and acetone. The day after admission, the left ear began to show a watery, white, purulent discharge. The temperature rose to 104.4° F. She was started on intramuscular penicillin, 10,000 units immediately followed by 5,000 units every three hours. The following day the temperature was 103.0° F. and the discharge from the ear continued. Sulfadiazine, 0.1 Gm. every four hours, was begun. Because of questionable nuchal rigidity, a lumbar puncture was done and completely normal spinal fluid was recovered. On the following day, the fourth day of hospitalization, the patient was observed to be jaundiced. Examination of the blood at that time showed the following: red blood cells, 2.24 million per millimeter;^{3} hemoglobin, 5.5 Gm. per 100 c.c.; hematocrit, 23 per cent; white blood cells, 26,200 per millimeter^3; polymorphonuclears, 26 per cent, lymphocytes, 68 per cent; monocytes, 6 per cent; and nucleated red blood cells, 2 per 100 leucocytes. The red cells were normochromic with mild anisocytosis and poikilocytosis. No spherocytes were seen, but there were occasional target cells. Urinalysis showed urobilinogen to be present in 1:5 dilution but bile could not be detected. The benzidine test for blood was 4 plus, and 15 to 20 red blood cells per high power field were observed on microscopic examination. Bleeding time was 4 minutes, 20 seconds, and the clotting time was 1 minute, 10 seconds. The blood Van den Bergh reaction was immediate direct and the icterus index was 130 units. The cephalin-cholesterol flocculation test was plus-minus. The patient was given a transfusion of 50 c.c. of typed and cross-matched Rh-positive, type O, citrated whole blood. The sulfadiazine was discontinued. On the fifth hospital day, the stained blood film showed many typical sickle cells. A moist preparation then showed marked initial sickling and 80 per cent sickling after incubation for twenty-four hours. No cold hemagglutinins could be demonstrated. The parents were blood-typed with the following results: mother was type A, Rh-positive, and father was type B, Rh-positive. The fever persisted at about 102.4° F. and the left ear continued to drain. On this day the hemoglobin was 7.0 Gm. per 100 c.c. and there were 2.08 million red blood cells per millimeter.^{3} Examination of the stained tibial marrow performed on the seventh day revealed marked sickling of the erythrocytes. At this point all available members of the patient's family were called in and moist blood preparations were done on each. There were both parents, the sole sibling, and a maternal uncle, none of whom showed sickling after twenty-four hours, nor could any familial history of anemia be obtained. On the eighth day, the hemoglobin was 6.5 Gm. per 100

c.c. and there were 2.45 million red blood cells per millimeter.[3] The ear had returned to normal by the ninth day, and, as the baby had been afebrile for the previous two days, penicillin was discontinued. The hemoglobin was 5.5 Gm. and there were 1.24 million red blood cells. Transfusion of 90 c.c. of citrated whole blood was done. The temperature remained normal and the child ate well until the twelfth hospital day, when the temperature again rose to 103.8° F. Physical examination at this time was negative except for the persistence of the icterus. The temperature returned to normal in two days without treatment. On the fifteenth day the child began to have diarrhea and to refuse feedings. A moist preparation of the peripheral blood made at this time showed marked sickling. The next day she was observed to moan constantly and seemed to have an expression of anxiety and pain. There was a gross increase in the degree of jaundice. A tubular mass could be palpated emerging from under the inferior edge of the liver in the right upper quadrant and descending to within 2.5 cm. of the level of the umbilicus. Hemoglobin was 9.5 Gm. and there were 3.05 million erythrocytes. Leucocytes numbered 19,900, of which 78 per cent were neutrophiles. Fully realizing that this development might be a manifestation of the sickle cell crisis, still the possibility of a surgical abdomen could not be ruled out. Later the same day, the skin overlying the mass became reddish-blue and the child began to exhibit symptoms of respiratory distress. Surgical consultation was obtained and a laparotomy was decided upon. After supportive therapy by whole blood transfusion and intravenous electrolytes, the abdomen was explored. Large mesenteric lymph nodes were the only abnormalities found. The downhill course continued postoperatively and exitus occurred after six hours.

On autopsy, it was seen that the child was markedly icteric. There were numerous ecchymotic areas over venipuncture sites.

The trachea showed an edematous and congested mucosa. The lungs were pinkish-grey in color with many whitish areas over all surfaces. These areas were from one to 10 mm. in diameter and slightly raised above the surrounding surface. On section, the whitish plaques were seen and the alveoli and smaller bronchi exuded a whitish—reddish—yellow thin fluid. The esophagus had a yellowish-gray mucosa, and, in its lower third, there were numerous areas of punctate hemorrhage. The pericardial sac contained some bile-stained fluid. The heart was of normal size, but very pale pink in color. The myocardium, on section, was pale.

On opening the abdominal cavity, the intestines were seen to be distended. Numerous areas of hemorrhage were seen throughout the serosa. The liver was slightly enlarged, and, on section, exhibited a pale brown parenchyma with bile-stained canaliculi. The spleen was slightly enlarged, had a thin, smooth capsule, was reddish purple in color, and had a firm consistency. On section of the spleen, a mottling was observed with areas of brown and deep red coloration. The stomach contained about 50 c.c. of chocolate-colored viscid fluid when opened. The mucosa was grayish, had engorged vessels, and showed numerous punctate hemorrhages. The small bowel showed moderate injection of the mucosal vessels. At the terminal end of the ileum were noted small grayish discrete areas disseminated over the mucosa and continuing into the large bowel as far as the distal portion of the descending colon. The kidneys were enlarged, grayish-yellow in color, with many wedge-shaped dark purple areas. Punctate hemorrhages were found all over the cortical surfaces. When sectioned, the pyramids and papillae were found to be bile stained. There were thromboses of the interlobar arteries. Areas of bipolar infarction were seen in both kidneys. The adrenals showed hyperemic medullae. The mesentery was greatly injected.

The lymph nodes were enlarged, but showed no gross invasive tendencies. There was a marked hemorrhagic cystitis of the bladder trigone, and spotty small hemorrhages of the rest of the bladder mucosa. The ureters were greatly dilated and hypertrophied, with a swollen ostia and diffusely thickened purplish-red hemorrhagic mucosa. There was a stenosis of the ureteropelvic junction on the left side.

Microscopic examination of sections of the spleen and kidney showed occasional typical sickle cells. Dr. Peter Vogel, the consulting hematologist to this service, who examined the tissue sections and the films of the peripheral blood and tibial marrow taken during life, confirmed the presence of typical sickle cells.

COMMENT

We have presented a case of sickle cell anemia. Two unusual features combine to make this case worth reporting. The first feature, the early onset at one month of age of sickle cell anemia in crisis, has not been previously described. It is likely that the hemolytic crisis in this case was precipitated by an infectious process, acute purulent otitis media. While chemotherapy and penicillin controlled the infection in a reasonable period of time, yet once the hemolytic process had been established, its course became rapidly progressive despite supportive therapy. The second noteworthy feature was the disparity between the amount of sickling observed in the early wet preparations during life, when 80 per cent of the red blood cells sickled in twenty-four hours, and the later wet preparations and the tissue sections obtained post mortem. In the latter, while some sickling was obvious, it was much less in degree than previously. It may be that the transfusion of normal erythrocytes plus the hemolysis of the patient's cells so diluted the abnormal forms as to account for this apparent decrease in the percentage of cells showing sickling. On a quantitative basis, the child's blood volume has been calculated as about 400 c.c. and the amount of whole blood transfused into the patient was measured at 315 c.c. Thus it may be seen that better than 75 per cent of the patient's blood volume at the time of death consisted of normal cells. All the transfused blood was freshly drawn and may be considered to have an expected viability of at least thirty days, about twice the period over which the transfusions were given.

The accessory evidence of a hemolytic process, essential for the diagnosis of sickle cell anemia in crisis, was present in our patient. The rapid reduction of hemoglobin content of the blood from 11.5 Gm. on admission to 5.5 Gm. on the fifth hospital day; the development of concurrent clinical and laboratory evidence of marked icterus; and the plus-minus cephalin-cholesterol flocculation test are indicative of rapid hemolysis and jaundice of extrahepatic origin. In passing, it should be remarked that sickle cell anemia in crisis is not infrequently accompanied by symptoms and signs referable to the abdomen and simulating an acute surgical emergency. In our case the masquerade was so effective that laparotomy was done. We have purposely refrained from commenting upon or stressing the patient's race because of the impossibility of accurately evaluating its true status.

SUMMARY

A case of fatal sickle cell anemia in crisis in a one-month-old Puerto Rican female infant has been presented. The development of the hemolytic crisis followed the occurrence of an acute purulent otitis media. Clinical and laboratory evidence confirmed the diagnosis.

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ENCEPHALITIS ASSOCIATED WITH HERPES ZOSTER

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POSTINFECTIOUS encephalitis complicating the acute exanthematous diseases is a relatively common occurrence, but encephalitis associated with herpes zoster is a rare event, even though the close relationship between the virus of chicken pox and that of herpes zoster has been recognized for some time. The following case is, therefore, of interest.

T. S., a white male child, aged 6 years, was admitted to St. Vincent's Hospital, Staten Island, on Aug. 7, 1946, with complaint of drowsiness, paralysis of the right side of the face, and weakness of the right leg. He had been well until four days prior to admission, when he began to run a low-grade fever and to complain of frontal headaches. On the day before admission, the mother had noticed a "rash" on both buttocks. These symptoms continued until the day of admission, when the right facial paralysis and weakness of the right leg was noticed and the family physician recommended hospitalization.

On examination, a fairly well-nourished and well-developed boy was noted, who appeared to be only moderately ill. The temperature was 101.6° F., respirations were 30 per minute and pulse was 120 per minute. The patient appeared to be quite restless, but was yawning constantly. Although he seemed quite alert, he was able to answer only yes or no to questions. There was right facial palsy and a positive Babinski reflex on the right side. The fundi were hyperemic, but otherwise normal. Herpetic lesions were present on both buttocks in areas corresponding to the cutaneous distribution of the second and third sacral segments. The spinal fluid was clear and showed no increased pressure. The cell count was 0, Pandy test was negative. The sugar was 50 mg. and the chlorides 660 mg. The red blood count and hemoglobin were normal, but the leucocyte count was 3,700 per c.mm. with the following distribution: small lymphocytes 14 per cent, mononuclears 6 per cent, polymorphonuclear neutrophiles 79 per cent, and plasma cells 1 per cent. The spinal fluid Wasserman and colloidal gold tests were negative. The urinalysis was also negative.

On the following day, in addition to the above findings, the patient exhibited a complete right hemiparesis, as well as incontinence of urine and feces. Another spinal fluid examination showed no abnormal findings. A diagnosis of a Strumpel-Lichtenstern encephalitis associated with herpes zoster was made. Treatment consisted of intravenous hypertonic glucose, as well as intensive vitamin B complex and vitamin C therapy.

The patient continued to run a low-grade temperature for a week. A Vollmer patch test was negative. Three days after admission, the superficial and deep reflexes returned on the right side, and on the next day he began to move his right arm and leg, although the right Babinski reflex was still present. The right facial paralysis was less pronounced and the incontinence was no longer absolute.

The patient was discharged to his home for further convalescence eighteen days after admission. A physiotherapeutic regime of massage, galvanism, and active and passive exercise of his right arm and leg was instituted. He was seen one month after discharge. It was noted that he was walking, but did not have complete range of motion of his right foot. The right fingers were flexed and spastic and he had difficulty in moving them and in grasping. The right facial palsy had nearly cleared. He still showed a moderate motor aphasia, but no

sensory aphasia. It is felt that it is too soon to evaluate this case as to the degree of permanent paralysis, Parkinsonism, behavior problems.

Of interest in the case is an apparent familial susceptibility to a neurotropic virus. Two days after this patient was admitted to the hospital, the family physician reported that another sibling, aged 2 years, had developed bilateral herpes zoster over the same areas as her brother. This did not progress to a clinical encephalitis. In May, 1946, a first cousin of the patient, a white male child aged 11 months, died of a measles encephalitis after an illness of about a week.

A cursory review of the literature does not reveal any case reports of this syndrome occurring during childhood. The case reported by Krumbolz and Luhan[1] was that of a 58-year-old woman. Thalhimer's[2] patient was 72 years old and Biggart's and Fisher's[3] was 63 years old. The only case with comparable sequelae was the one reported by Bellavitis[4] in a psychotic patient age 53 years, who had suddenly developed herpes zoster in the distribution of the second to the fourth cervical segments on the left side. Eight days later, palsy of the peripheral type developed on the same side of the face and a few days later hemiporesis developed on the left side. In all of these cases, cerebral symptoms developed more than a month after the onset of the herpes, in contradistinction to our patient, whose cerebral symptoms coincided with the onset of the eruption.

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The Academy Study of Child Health Services

A REVIEW OF PROGRESS AND A PREVIEW OF PLANNING

Having been present when the Academy's Study of Child Health Services was first placed upon the planning boards, having attended its launching upon rather uncertain seas at the annual meeting in Detroit early in 1946, and having watched its development from the position of sponsor and adviser, it seems appropriate and timely to review its progress and also to gaze into the crystal in an attempt to see where we may be at the end of another year.

Annual meetings of the Academy present an excellent opportunity to take stock of the progress which has been made and to build upon the steps already surmounted, others leading toward further endeavors. The meeting held recently at Pittsburgh emphasized two significant facts. First, the Academy's Study had grown far beyond the anticipations which even its most enthusiastic proponents originally expressed. Second, the efforts of its members, both singly and collectively, during the preceding year had brought the Academy into a position of prominence and responsibility which demanded energetic planning if it is to make full use of the wealth of factual data now becoming available.

A little over one year ago, at our meeting in Detroit, Dr. John Hubbard, who had only a short time before been appointed director of the Academy's Study, brought before the meeting the plans which had been evolved to launch this project upon a nation-wide scale. The responsibility of obtaining the desired information was placed in the hands of State Chairmen. This responsibility was accepted with considerable misgiving. Indeed, there were those who questioned if the job could be done at all. Now, however, although the Study is not completed, it has gathered such momentum that it would be impossible to stop it. It was reported at Pittsburgh that the Study had been organized and was being successfully pursued in all States, including the District of Columbia and the Territory of Hawaii, with the single exception of one State, which it is hoped will follow soon. About a dozen States have completed the collection of information and have sent their questionnaires to the Central Office for statistical analysis. It is expected that all States will complete the collection of information by July of this year.

The first tangible results of the Study came to light at Pittsburgh in the form of a weighty volume which was distributed as a preliminary draft of the Study of Child Health Services in North Carolina, our "pilot" State. This was put into the hands of the Executive Board, the Academy Committee, and all State Chairmen who attended the meeting. It has since been distributed to all members of the North Carolina Pediatric Society. On March 12, 1947, it was the subject of a lengthy conference at a meeting of the Advisory Committee. It now becomes the responsibility of the pediatricians of North Carolina and a committee which they have appointed to reduce the overwhelming mass of factual data to more appropriate dimensions and to prepare the recommendations intended to serve as a basis for a continuing program.

While the State Studies have been reaching successful completion, the second main division of the Academy Study, the Study of Pediatric Education, has been developed under the able direction of Dr. John Mitchell. Regional meetings, which have been held throughout the country by Dr. Hubbard and Dr. Mitchell, have been attended by the chiefs of pediatric departments in their respective areas in order to introduce to them the plans and purposes of this phase of our work. Personal visits have now been made to about half of the medical schools and the major teaching hospitals of the country. From these visits a wealth of information is pouring in to the central office of the Study. When this material is analyzed and summarized, it should afford a composite and yet detailed picture of pediatric education never before available.

At this point, with the success of the Study assured and with the data on all phases of child health services well along the way toward analysis, the most important question of all demands an answer. What is to be done with all this information when it has been summarized in a final report? It is no mere coincidence that a new committee of the Academy has already been formed and charged with the responsibility of writing an answer to this question. As long ago as last fall, Dr. Lee Forrest Hill, then President-elect, recommended, first in a meeting of the Committee for the Study of Child Health Services, and shortly thereafter in a meeting of the Executive Board, that this new committee should be appointed without delay, in order that it might overlap with the Study committee and serve as a continuing committee for the implementation of the Study. This new committee, which is to be designated as the Committee for the Improvement of Child Health, met in joint session with the old committee at Pittsburgh. At this meeting, the Academy projected its planning to the point when an action program may be developed upon the basis of the survey material. Thus the Academy has demonstrated that it has recognized its increased responsibility and has given assurance that it has every intention of making proper use of the available information at both State and National levels. The policies and procedures which have been established to govern the reporting and implementing of the Study have been expressed in the following series of recommendations which were drawn up by the Committee for the Study of Child Health Services, submitted to and approved by the Executive Board in November, 1946:

1. That all factual material arising from the Study of Child Health Services should be released by the American Academy of Pediatrics at both National and State levels.
2. That the Committee for the Study of Child Health Services is responsible not only for preparing a National Report of the factual material but also for submitting to State Chairmen tabulated factual data suitable for the preparation of State Reports.
3. That State Chairmen, together with their Advisory Committees, are responsible for seeing that State Reports based upon the tabulated material are written and published as soon as possible. Whereas the National Report prepared by the Committee for the Study of Child Health Services will include no recommendations arising from the data, the State Reports may and should include recommendations based upon local situations.
4. That when the tabulated material is received by the State Chairman he will confer with the State Medical Society, the State Dental Society, and the State Health Department regarding the interpretation and use of the material, in those States where these agencies have cooperated in the conduct of the Study.
5. That within a period of two months after receipt of the tabulated material, State Chairmen should be required to submit to the Committee for the Study of Child Health Services a statement indicating that definite plans have been made to write a State Report and a brief description of such plans. If, at the end of this two-month period, the State Chairman has not made satisfactory plans to report the material arising from the Study in his State, the Committee for the Study of Child Health Services is free to release the factual data to any person or group qualified to use it within the State. If the plans for the preparation of the State Report are considered by the Committee to be satisfactory, then the State Chairman should be allowed an additional period not to exceed four months to complete the State Report, during which time none of the factual data pertaining to his State should be released to others by the Committee for the Study of Child Health Services except after obtaining approval from the State Chairman concerned.
6. That after a period of six months following the receipt by the State Chairmen of the tabulated material, the Committee for the Study of Child Health Services is free to release the tabulated material or punch cards to any person or group qualified to use it.
7. That a further Committee of the Academy should be created which would be responsible for the recommendations arising out of the Study at the National Level and for developing from the Study a suitable action program. This committee would

also be responsible for reviewing the recommendations contained in State Reports, advising in the use of the material in the respective States, but would have no veto power over any recommendations in State Reports.

8. That in the case of North Carolina, the pilot State, the Committee for the Study of Child Health Services should be responsible not only for the factual report but also for reviewing the recommendations contained therein.
9. That in publication of State as well as National Reports, credit should be given to the United States Public Health Service and the Children's Bureau for the cooperation they have given to the Academy in the Study. Acknowledgment should also be made of contributions or cooperation in the form of services and financial support from other sources.
10. That after publication of National or State Reports the factual material should be available to anyone desiring to use it.

As a member of the Committee on Child Health Services and as a resident of Washington, it has been my privilege to know rather intimately of the work of the Study from its early inception up to the time of this report. As an observer in this strategic position, it is gratifying to record and emphasize the remarkable spirit of cooperation and accord which permeates the whole Study group, now numbering several score.

Furthermore, the Study represents a rather unique and original experiment in the active cooperation of governmental agencies with a purely voluntary organization, not for the individual aggrandizement of any component, but toward the attainment of a common goal "for the improvement of child health," a purpose made dynamic by the very phraseology of the term, which has wisely been chosen as the caption for the newly appointed continuation and action committee of the Academy.

At its St. Louis meeting, the Academy unanimously decided to embark upon this nation-wide investigation of the needs of children and to develop the ways and means of meeting them.

With the realization that the Study was to be conducted by pediatricians in the interest of children and pediatrics, it became apparent from the onset that aid would be imperative from professional members of governmental agencies who were skilled in the techniques of exploration in the field of child health.

By direction of the original resolution adopted by the Academy, the Children's Bureau and the U. S. Public Health Service were asked to lend assistance, which was instantly and generously granted on the part of both agencies. Any misgivings on the part of pediatricians or other physicians (and there have been some) that the participation of governmental agencies in the undertaking at hand inferred ulterior motives of dominance in the field of health services to children would be set at rest were such questioners familiar with the facts. The outstanding fact apparent to the Academy's committee is that the successful completion of the Study would have been utterly impossible had it not been for the contribution of that endowment of expert knowledge, that "know-how" of trained investigators and statisticians (which not even the most robust academician could justly claim to possess) generously given us by the assisting agencies.

In monetary value of services rendered alone, this represented thousands of dollars aside from the substantial financial aid of the grants which have been received.

One outcome of the Study stands forth as a prophetic omen for the future, namely, the accord and harmony which may and should be the bond of cooperation among all who labor for the improvement of the health of children and for the progress of pediatrics which is their servant.

The Study of Child Health Services started as our responsibility; it continues as our opportunity.

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The Social Aspects of Medicine

Dr. Ernst P. Boas of New York, N. Y., chairman of the Physician's Forum, has been kind enough to reply to Mr. W. A. Milliman's "Compulsory Prepaid Medical Care" (J. Pediat. 29: 527, 1946). Mr. Milliman's article should be reviewed in order to understand fully Dr. Boas' answer.

E. A. P.

COMPULSORY PREPAID MEDICAL CARE

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Compulsory prepaid medical care under governmental auspices is a technique of providing medical care to all the people. Intelligent discussion of this controversial subject involves a consideration of the basic social philosophy that has persuaded many persons that good medical care should be universally available, as well as an evaluation of the feasibility of assuring good medical care to all by means of this method.

During the past decades, the public, the recipient and purchaser of medical care, has become ever more aware of the potentialities of modern medicine in the prevention and treatment of disease, and has become ever more articulate in demanding that this great social service be made available to all, irrespective of income or buying power. This view has been given forceful expression in Franklin D. Roosevelt's new Bill of Rights in which "The right to adequate medical care and the opportunity to achieve and enjoy good health" are laid down as basic human rights. This paper is based on an acceptance of the tenet that availability of medical care is a fundamental human right.

It has been well established that good medical care is out of reach of large numbers of our citizens because it is beyond their financial capacity. This is not the place to present the voluminous factual data to support this statement, they are readily available to all who wish to seek them out. Mr. Milliman, in his recent article, "Compulsory Prepaid Medical Care" concedes that much of this is true. Unless we regard medical care as a luxury, which people may or may not obtain, depending on their ability to pay for it, we are faced with the compelling problem of how to make it available to all, irrespective of income. It is at this point that many persons leave the cold path of logic, and, rationalizing their fear or dislike for an extension of governmental responsibility, seek to find a solution in halfway measures, such as the establishment of voluntary health insurance schemes, and the construction by government of hospitals and diagnostic centers.

Yet, the role of government in preventing disease and treating the sick is an ancient one. No one today challenges the duty of government, through its public health agency, to continue to marshall every resource to prevent epidemics and control infectious diseases. No one would wish government to cease providing medical care for the indigent, and for patients with certain chronic diseases, whose course is so long drawn out that the patients and their families cannot afford to pay for this care. I refer to mental illness and tuberculosis.

The diseases responsible for most sickness and deaths today are no longer the infectious diseases such as typhoid fever, tuberculosis, and the acute exanthemas. They are diseases obscure in origin and chronic in their course, such as the several forms of heart and arterial diseases, diabetes, cancer, rheumatoid and other forms of arthritis. None of the conventional methods of preventive medicine will ward off any of these disorders. The public health officer is learning that in order to control their ravages—for in the present state of medical

knowledge their prevention is still beyond the range of medical science—the most potent weapon is immediate and ready accessibility to medical care, both for diagnosis and treatment. This is why thinking health officers have become deeply concerned with the quality and availability of medical care, and why many of them do not hesitate to advocate radical changes in the economic pattern of medical practice. Fundamentally, this, too, is not a new concept. In his attempts to prevent tuberculosis and venereal diseases, the health officer has been compelled to undertake the treatment of sufferers from these diseases. Indeed, he has gone further, and, by examining the families and others who have had contact with victims of these diseases, has offered diagnostic and therapeutic services to persons who were presumably well, all in the effort to prevent disease.

The changing face of disease, brought about by the rapid and efficient control of the infectious diseases, has brought about a new and necessary reorientation of public health activities. If making medical care readily available to all will help to control the rapid evolution of some of the chronic diseases and maintain many persons as useful economic units of society, there is every reason for government to concern itself with the problem through the agency of its public health services.

This need not involve total regimentation of medical services in the nation, or complete shedding of personal responsibility for the maintenance of individual health. But government must assume leadership, provide facilities of public education in disease control and the utilization of medical facilities, and collect and administer the funds that are needed to provide adequate medical care for all.

If we face the changing order in medicine and in society with realism and honesty, we must seek to discover by what methods good medical care can be made available to all inhabitants of this country. Mr. Milliman suggests that the best progress in improving preventive medical care would be achieved by further emphasizing medical research, by improving facilities for medical education, and by expanding and improving existing public health services. He does not indicate from where funds for these purposes will be obtained. He also advocates the development of diagnostic centers financed in part by public funds, in part by charity, in part by charges for services. He suggests further experimentation with voluntary plans for prepayment of medical costs, the development of a more constructive attitude by the medical profession, and experimentation with group practice. These all are excellent suggestions as far as they go.

Funds for research for medical education have been derived largely from philanthropic foundations and from wealthy donors in the past generation. It is apparent that this source is rapidly becoming inadequate to meet the growing needs. Lower interest rates on capital funds, and greater taxation have greatly decelerated the growth of fortunes. Ever greater dependence must be placed on tax funds.

Voluntary prepayment insurance for medical care can never meet the needs of the bulk of the population. This has recently been forcefully demonstrated by Goldman.[2] He shows that, judged by the criteria of the provision of early diagnosis and treatment, completeness of medical care, quality of service, and cost to the patient, only the few voluntary prepayment plans organized on the basis of group practice are making real progress or rendering good service. The large majority of prepayment plans, in which the individual doctor is compensated for certain individual services that he renders, are nothing but financial arrangements for payment of bills, and do not improve the quality of medical care. A good prepayment plan for complete medical services given through group practice units costs from $25 to $30 a year per person—a price beyond the reach of many heads of families. It is interesting to recall that the minority report of the Committee on the Costs of Medical Care, signed by representatives of the American Medical Association stated: "Nothing has been made clearer than the fact that voluntary insurance schemes have everywhere failed. It seems clear, then, that if we must adopt in this country either of the methods tried out in Europe, the sensible and logical plan would be to adopt the method to which European countries have come through experience, that is, a compulsory plan under government control."[3]

It is both experience and the inexorable logic inherent in the situation that compel the conclusion that adequate medical care for all can be achieved only by means of universal compulsory prepayment insurance or by a system of state medicine. State medicine has no advocates in this country; it is unsuited to our traditions and customs and could hardly be successful today. That leaves compulsory health insurance as the only alternative. Let us try to determine whether such a compulsory insurance system is technically feasible, whether it has the potentialities of good medical service.

Mr. Milliman has many doubts. He fears that so many controls would have to be instituted by the administrator that "they would result in unforseen changes in the present bases of the practice of medicine." While I would agree that overcentralization and overstandardization would be bad, I do not believe that these evils are inherent in compulsory insurance. Decentralization and local autonomy in professional matters are essential and can be achieved. A practicing physician, with clinical contacts with great numbers of physicians and patients, I am acquainted with the great deficiencies of medical practice today, due in part to the fact that patients have not enough money to obtain needed special services, in part to lack of knowledge of some physicians, in part to the business side of medical practice which obtrudes itself into matters that should be purely professional. I believe it unwise to follow a laissez-faire policy for fear of the possible evils of certain controls; indeed it would seem that certain controls are highly desirable. Mr. Milliman fears that such controls may "fundamentally alter many features of the present system of medicine and medical economics." I hope they will.

The fee for service system of compensation of physicians under any form of prepayment plan is unworkable and will lead to abuses and much red tape. It will lead to overtreatment and overcharging by unscrupulous physicians to the detriment of honest physicians. There is no reason why the capitation or salary system of compensation should not be satisfactory. Unquestionably the average income of physicians would be increased, if for no other reason than that they would be paid for caring for patients whom they now treat free of charge. It is true that the inflated incomes of some specialists would, in the course of time, greatly diminish, but this is not, from the point of view of the public, an unmitigated evil. I will never believe that the best of our doctors, or indeed the majority of them, enter the practice of medicine with the prime purpose of earning large incomes. Today our standards of success in medicine are false—we respect the wealthy surgeon and practitioner who aspires to social equality with the banker or industrialist. It is high time that the profit motif be taken out of medicine. To say that as a result of this there would be a dearth of competent young men entering the profession is to malign all of the traditions and ideals of medicine. Even today, in a highly competitive commercial world, many of the best of our physicians enter salaried careers in universities, in the U. S. Public Health Service or in analogous fields.

Mr. Milliman is of the opinion that so many physicians would refuse to participate in a plan of compulsory health insurance that it could not be operated properly. With this statement I must disagree. Even in these prosperous times, I have yet to see an adequately salaried position in industry, in a hospital that cannot be filled many times over, or any medical plan of a labor union or a fraternal society that cannot obtain as many doctors as it needs, in spite of the inevitable deficiencies of almost all such enterprises. Hosts of physicians still lack economic security and grasp at any added source of income. Moreover, among the younger generation there are many who would welcome compulsory health insurance.

It is true that today there are not enough doctors, dentists, and nurses to give full medical care to all of the people. Their numbers suffice today because many needed services are not given to patients who cannot pay for them. This is no argument against compulsory insurance. It should rather be an impelling motive to increase the number of well-trained physicians, dentists, and nurses, until there are enough to minister to the needs of the country. The passage of an insurance act would accelerate this greatly needed recruitment of medical personnel.

Reference is made to the violent opposition, especially of the more competent members of the medical profession, and it is suggested that their cooperation cannot be obtained if the proponents of the health insurance measure continue to exhibit the lack of candor which they have manifested in the past. I do not believe that the sponsors of this legislation have shown lack of candor; they may have erred in some of their decisions, particularly in those in which they tried to appease the medical profession. The most striking example of this is the retention in the last bill of the fee-for-service payment to doctors. To my mind and to the minds of many others, it is the medical profession itself that has shown lack of candor. The *Journal of the American Medical Association* has not opened its pages to the proponents of compulsory health insurance, and has deliberately slanted its news and editorial features to give a very one-sided view of the issue. The National Physicians Committee, whose activities have been approved and applauded by the American Medical Association, has gone much further in actual distortion of the truth and obfuscation of the issues in its printed material that has been scattered over the land.

As a physician with a great pride in his profession, it is my guiding purpose to assist in making the best medical care available to all. A plan that would make mediocre or poor medical care more widespread than it is today could hardly arouse my enthusiasm or support. Even with little change in medical organization, compulsory medical care insurance would tend to improve medical care by removing the financial barrier between doctor and patient; from the point of view of costs, at least, it would place at the disposal of the practicing physician all of the resources of modern medicine in the service of his patients. But this is not enough.

It has become a truism that the best medical care is given by physicians cooperating in a well-knit group, the services of the group being purchased not by a fee paid for every service, but by a prepayment plan. Such group service must be incorporated in a compulsory insurance plan, as indeed it was made possible in the last Wagner Murray Dingell Bill. Service by groups, in addition to providing better medical care, will go far to simplify the administrative features of such a plan. The insurance fund can make contracts with the group to take responsibility for large blocks of patients. The moneys would be paid to the group, which, by a democratic procedure, could decide how the compensation of the individual members of the group would be allocated. Within the framework of the broad standards set by the central administration, the group would be completely free to recruit its members, assign them responsibility, provide for their particular interests, and conduct all of its professional affairs.

It would be folly, indeed it would be disingenuous to assert that any individual, group of individuals, or organizations, whether lay or medical, can write a perfect bill free from all defects, that will bring the millennium in the field of medicine. But it is high time that physicians become aware of the changing order in science, in medicine, and in society, and that they give their best brains and efforts, not to delaying tactics or sabotage but to the end that in the foreseeable future excellent medical care will be available to all of the people of the United States.

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Academy News and Notes

THE FORMATION OF THE BRAZILIAN BRANCH OF THE AMERICAN ACADEMY OF PEDIATRICS

In May of 1942, Dr. Adamastor Barboza, at that time in Washington, D. C., as delegate of Brazil at the Eighth Pan-American Child Congress, arranged with the secretary of the Academy to extend activities of the Academy to all South American countries and ask for the concerted help of Brazilian pediatricians toward this end. It was agreed that at a suitable time in the immediate future, the plan then being elaborated by the Academy should be reconsidered.

The names of a few Brazilian pediatricians were submitted for acceptance as active members in the Academy with exactly the same privileges and duties as the North American members. The qualifications for eligibility to fellowship were the same as those observed for all regions of the Academy: (a) professional integrity; (b) activity exclusively in pediatrics, in practice, teaching, or public health work, or combinations of these; and (c) at least five years of practice in pediatrics.

Two types of annual dues were set up provisionally. One of these is $5.00, including the member's privilege to receive in Spanish abstracts from two main American reviews on pediatrics—"The Journal of Pe. .trics" and "The American Journal of Diseases of Children." A second is $10.00 with a full subscription to "The Journal of Pediatrics" and abstracts in English of the original articles published in "The American Journal of Diseases of Children." It was suggested that the second type already adopted by the pediatricians of Mexico would possibly be the more interesting.

The following list of pediatricians was submitted:

Dr. José Martinho da Rocha
Dr. Leonel Gonzaga
Dr. Mario Olinto
Dr. Cesar Pernetta
Dr. Lages Netto
Dr. Alvaro Aguiar
Dr. Carlos Florencio de Abreu
Dr. Adamastor Barboza

In November, 1942, a committee of five was formed whose function would be to pass upon the qualifications of any wishing to apply for membership in the Academy. In order to link the activities of the Brazilian Committee of the Academy with the Sociedade Brasileira de Pediatria, a conference was held with Dr. Vicente Lara, President of the Pediatrics Division of the Medical Association of São Paulo, suggesting the possibility of the formation of a mixed committee with representatives from both the Sociedade Brasileira de Pediatria and its sister Society in São Paulo.

A subcommittee consisting of Dr. Adamastor Barboza, Dr. Eduardo Imbassahy, and Dr. Alvaro Aguiar was formed. This committee decided unanimously to form a Brazilian Committee of the American Academy of Pediatrics, whose membership should be chosen from the eight pediatricians recently suggested to the Academy. To avoid any partisanship, it was decided to limit the choice to those who had already filled the post of president of the Sociedade Brasileira de Pediatria.

As a result, the first Brazilian Committee of the Academy consists of the following members:

Dr. José Martinho da Rocha
Dr. Mario Olinto
Dr. Cesar Pernetta
Dr. Leonel Gonzaga
Dr. Adamastor Barboza

One of our members, Dr. José Robalinho de Oliveira of Pernambucco, Brazil, died recently.

News and Notes

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES ANNOUNCES AN EXTENSION OF ITS CHILDREN'S DIAGNOSTIC SERVICES

An extension of the diagnostic service of the Children's Tumor Registry of Memorial Hospital was made on Jan. 1, 1947, with the establishment of the Children's Diagnostic Clinic. This service is offered to the pediatric patients of hospitals and private physicians for the diagnosis of neoplastic diseases, and is available for ambulant or bed cases. The investigations will be performed at cost or without charge if the patient is unable to afford this. Upon completion of the study the patient will be referred back to the physician or institution interested, with a report of the findings. If therapeutic recommendations are indicated and requested they will also be made.

Appointments for such examinations may be made by mail or telephone with: The Secretary, Pediatric Service, Memorial Hospital, 444 East 68th St., New York 21, N. Y.

NOTICE

Due to the increased cost of running the *American Board of Pediatrics*, the board has found it necessary to raise the application fee to $125.00, effective May 1, 1947.

Book Review

The Challenge of Polio. R. H. Berg, New York. 1946. The Dial Press.

This little volume, written under the auspices of the National Foundation for Infantile Paralysis by a nonmedical, professional science-writer, serves its primary purpose fairly satisfactorily, which is to acquaint the public with the problem of poliomyelitis in a readable style. While, like most other attempts to present scientific or medical subjects for lay readers, the book leaves one with a feeling of dubiousness regarding some of the contributions singled out for special emphasis, it impresses the reviewer as being fair and authentic on the whole.

The historic development of our knowledge of the disease, the discovery of its cause, studies on its epidemiology or mode of spread, and the attempts to find effective means for its prevention and treatment are interestingly reviewed. One fact brought out which should arrest the attention of the professional as well as the lay reader is that severe epidemics of poliomyelitis were not known before the latter part of the nineteenth century. The author makes it clear that the increasing frequency of severe epidemics during the past thirty years presents a grim challenge to medical scientists. While the conspicuous gaps in our knowledge are clearly pointed out, recent advances are presented in a hopeful light. The appraisals of such controversial topics as the Kenny concept and treatment of poliomyelitis and neurotripsy are rational and without emotional prejudice.

From the pediatricians's viewpoint, the most glaring deficiency of the book, which is forsooth a reflection on current literature on the subject, is the almost total lack of reference to the 6 to 15 per cent mortality resulting from the acute disease. While space is freely devoted to consideration of the spinal paralytic type of case, no attention is given to the forms of the disease which result in respiratory and circulatory insufficiency or death and which terrify the physician as well as the patient and his family. The book's index does not include such terms as bulbar, cranial nerves, polioencephalitis, respiratory failure, respiratory muscles, diaphragm, intercostals, respirator, artificial respiration, pulmonary, atelectasis, edema, pneumonia, oxygen, anoxia, complications, or others that would indicate any insight into or interest in these more serious aspects of the disease.

I. McQ.

Comment

THE FIFTEENTH ANNUAL MEETING

Despite the postponement of the Fifteenth Annual Meeting from last November to February 24-27 of this year, the Pittsburgh meeting was the largest, and in many ways the most successful, ever held by the Academy. The total registration was 1,363 with 589 Fellows in attendance.

Round Tables, which had to be discontinued in large part during the war, were again included in the program. There were four half-day sessions of ten round tables each. The panel discussions, which were held at the same time, were of unusual interest and well attended. In fact, there were so many things of interest going on at the same time it was difficult to make a choice of what session to attend.

At the annual business meeting, the Borden Award was given to Dr. James Gamble of Boston in recognition of his years of fundamental research in infant metabolism. The 1945 Mead-Johnson Award, which was not presented last year, was awarded to Dr. Paul Harper of New Haven in recognition of his work in malaria control in the Pacific Area during the war. The 1946 Award went to Dr. Horace Hodes of Baltimore for his work on virus encephalitis during the war.

By a rather close vote, the plan presented last year was adopted for redistricting the Academy membership into nine districts of comparable membership size to replace the past division into four regions. Each district will have one member on the Executive Board. In place of the regional meetings, sectional meetings arranged by the central office will be held in different parts of the country. The next annual meeting will be held in Dallas, Texas, in December of this year, and the first of the sectional meetings in Salt Lake City, Utah, in September.

With Dr. Durand's retirement at the end of the meeting, Dr. Lee Forrest Hill assumed the presidency. Dr. John A. Toomey of Cleveland was elected President-elect.

Considerable time was given, in committee meetings and by the State Chairmen, to the Academy Study which is making rapid progress. A most important step was the announcement of a new committee headed by Dr. James Wilson to implement the results of the study. This committee of nine will have three-year terms with three new members annually. On its shoulders and those of the state chairmen will fall in large part the use that is to be made of the study.

With the Pepper Bill in the discard, there was nothing to upset the dispositions of the Fellowship, and, despite storms and late trains, many remarked that it was as good and successful a pediatric meeting as they had ever attended.

mal persons.[4] While the output of ingested pentose by a pentosuric lasts somewhat longer and is slightly greater than in a normal person, the blood pentose and glucose tolerance curves are similar.

Other laboratory procedures are applicable in identifying pentoses. Urines containing pentose reduce Benedict's qualitative solution at 50 to 60° F. in ten minutes, while urines containing as much as 4 per cent glucose fail to cause a reduction.[28] A pentose urine retains its reducing power at room temperature almost indefinitely, while a glucose urine will show greatly reduced reduction under the same conditions. dl-arabinose and glycuronic acid do not reduce Benedict's qualitative solution in the cold or at 55° F. An aniline acetate paper test is a good confirmatory test for pentose.[29] When very small amounts are suspected, increased elimination and identification may be elicited by the administration of pyramidon or the previously indicated drugs. The melting point of osazones is not a simple or necessary routine procedure but can be done for absolute identification.

SUMMARY

An instance of renal glycosuria and pentosuria occurring together in the same patient presenting symptoms of diabetes mellitus is reported. The importance of recognizing pentosuria occurring in a diabetic patient is emphasized. The laboratory procedures necessary for the identification of the disease entities are simple, available, and easily interpreted, and are accordingly indicated.

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POISONING DUE TO INGESTION OF WAX CRAYONS

Report of a Case

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REPORTS of aniline dye poisoning among infants are fairly numerous.[1-6] With the exception of one of the cases reported by Zeligs,[2] all of the patients have been infants poisoned by contact with diapers freshly stamped with material containing the aniline dye. The one exception among Zeligs' patients was a child who inhaled fumes from an aniline-containing material used to exterminate bugs.

The case reported here is that of a 38-month-old child who, after ingestion of wax crayons, developed symptoms of paranitraniline poisoning.

CASE REPORT

History.—The parents stated that at 6:30 A.M., June 22, 1946, the child, H., appeared quite normal when she awoke, and was talkative, responsive, and active. She was taken to the bathroom and returned to bed. She and her twin sister were dressed in bathrobes and slippers, and allowed to look at books in bed and to play alone in their room, as had been their custom. They were in a large, sunny nursery, containing nothing but the usual type of children's toys.

At 8:30 A.M., when their door was opened, the twins were both playing with a large box of crayons which they had obtained by climbing up to the top shelf of a closet. Many of the crayons were broken and stepped upon on the floor, and several showed evidence of having been chewed. H. was sitting in the middle of the floor, her pajamas off, very subdued and still, in marked contrast to her sister. Her skin was bluish, her fingernails and toenails deep blue, and her lips and mouth black. Her respirations were rapid. She did not talk when questioned, but her twin sister said, "She ate crayons." The mother thought at first that the child might have been chilled, despite the warm morning. However, she did not respond to being blanketed and, when lying in bed, had considerable difficulty in breathing, turning, twisting, and trying to sit up. Her respirations became increasingly rapid and labored, and her color increasingly worse. She was brought to the doctor's office at about 9 A.M.

Physical Examination.—The patient was very weak and listless, but mentally clear. The rectal temperature was 100° F., respirations 20 and pulse 180 per minute. The skin was slate colored, while the nailbeds and lips were almost black. The abdomen was negative, but the heart seemed enlarged to percussion. The mouth and throat were negative except for the extreme cyanosis. The eyes, ears, and nose were normal. There was nothing abnormal on neurological examination, except that the child was listless and sluggish.

The patient was rushed to the hospital, oxygen was administered immediately, and 1 cat unit of digitalis was given hypodermically. Her condition had improved after about an hour, and it was decided to have x-ray films made of the stomach for evidence of the crayons, and of the heart for size.

X-ray Report.—"There is a quantity of opaque material in the stomach and right lower quadrant. Heart and lungs are normal." (Fig. 1.)

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The patient became quite dyspneic and more cyanotic in the x-ray department, but improved perceptibly upon being returned to the oxygen tent. Improvement was gradual and oxygen was discontinued after thirteen and one-half hours. Other therapy consisted of parenteral administration of fluids, repeated enemas and laxatives, and gastric lavage. Pieces of crayon were obtained by the latter procedure and these, together with the stomach washings, were saved for chemical study. The child's condition improved steadily and she was discharged from the hospital forty-eight hours after admission. She was below normal in general activity and health for at least two weeks following the poisoning episode.

Laboratory Findings.—On June 22, 1946, hemoglobin was 12.5 Gm.; red blood cell count, 4,560,000; white blood cell count, 10,900; neutrophiles, 63 per cent; lymphocytes, 35 per cent; and monocytes 2 per cent. Urine showed a strong reaction when tested for acetone and diacetic acid. On June 24, hemoglobin was 12 Gm.; red blood cell count, 4,440,000; white blood cell count, 8,750; neutrophiles, 43 per cent; lymphocytes, 54 per cent; monocytes, 2 per cent; basophiles, 1 per cent. Urine was the same as on June 22.

The remainder of the laboratory examinations were done by one of us (H. B.).

Urine: Urine sampled eight hours after ingestion of the crayons contained bilirubin in the high amount of 2.2 mg. per 100 c.c. and urobilinogen more than twice the normal. One week later, 0.5 mg. per 100 c.c. bilirubin was found. The corresponding blood serum level was 0.5 mg. per 100 c.c.; direct reaction was negative.

The spectrophotometric examination of the urine did not indicate the presence of hemoglobin or methemoglobin.

Color reactions with Millon's reagent, ferric chloride, and bromine water were positive, thus indicating the presence of conjugated para-aminophenol (Table I).

Blood: The first blood pictures did not reveal significant changes. Further examination showed a moderate anemia which was disappearing after two weeks (Table II).

TABLE I. URINE FINDINGS

TIME AFTER POISONING	BILIRUBIN MG./100 C.C.	UROBILINOGEN DILUTION	PARA-AMINOPHENOL
8 hours	2.2	1:50	positive
24 hours	1.6	1:20	
1 week	0.5	1:20	
2 weeks	0.0	1:20	

TABLE II. BLOOD STUDY

TIME AFTER POISONING	HB (GM./ 100 C.C.)	RBC (MILLIONS)	RET. (%)	WBC	S (%)	E (%)	B (%)	L (%)	M (%)	BILIRUBIN MG. 100/C.C.	BILIRUBIN DIRECT
Day of poisoning	12.5	4.6		10900	63.0			35.0	2.0		
2 days	12.0	4.4		8750	43.0		1.0	54.0	2.0		
1 week	8.5	4.1		9800	42.5	6.5	1.0	46.5	3.5	0.5	negative
2 weeks	10.0	3.9	2.7	8700	38.0	4.0	1.0	50.0	7.0		
										THYMOL TURBIDITY TEST	
3 months	11.6	3.8		8750	36.0	7.0		51.0	6.0	negative	

Hb = hemoglobin; RBC = red blood cells; Ret. = reticulocytes; WBC = white blood cells; S = segmented cells; E = eosinophiles; B = basophiles; M = monocytes.

A blood sample, taken early enough to give evidence of methemoglobin formation, was not made available for examination.

Stomach Contents: The remnants of the crayons, removed from the stomach by lavage, weighed approximately 2 Gm.; they consisted mostly of red and orange pieces.

The stomach fluid was diazotized with potassium nitrite, beta-naphthol was added, and a red dye produced. The intensity of the color reaction proved the presence of appreciable amounts of primary aromatic amine.

Wax Crayons: A piece of red-orange crayon recovered from the vomitus was examined by a method used in the paint industry.[7] To one part of finely divided crayon, concentrated sulfuric acid was added; to another part, 10 per cent sodium hydroxide; and to a third part, saturated alcoholic potassium hydroxide solution. The reactions corresponded exactly to that of "light red paranitraniline."

The wax crayons used by the child and swept from the floor were "Crayola" crayons and "True-Tone Crayons."

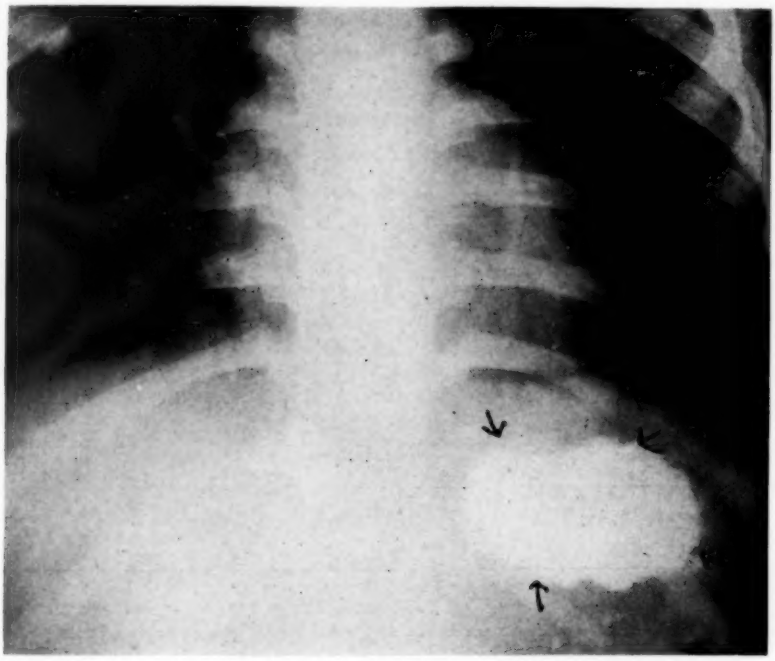

Fig. 1.—X-ray showing wax crayons in stomach.

EXPERIMENTAL STUDIES

In order to obtain information about this type of poisoning, additional examinations of wax crayons and animal experiments were conducted by one of us (H. B.).*

1. Orange and red crayons were examined for parared, an organic pigment made by coupling diazotized paranitraniline with β-naphthol. The results of the examinations are shown in Table III.

Orange crayon and red-orange crayons (two brands) contained parared, while the red and the yellow-orange crayons were free of it. As expected, no parared was present in green, yellow, and white crayons.

*With the assistance of Jeanne E. Mazur, M. A.

TABLE III. PARARED IN WAX CRAYONS

CRAYON	H_2SO_4	ALCOHOLIC KOH	70% HAc
Orange (B. & S.)	Positive	Positive	Positive
Red-orange (B. & S.)	Positive	Positive	Positive
Red-orange (T. T.)	Positive	Positive	Positive
Red (B. & S.)	Negative	Negative	Negative
Yellow-orange (B. & S.)	Negative	Negative	Negative
Green (B. & S.)	Negative	Negative	Negative
Yellow (B. & S.)	Negative	Negative	Negative
White (B. & S.)	Negative	Negative	Negative

2. To 10 c.c. samples of human gastric fluid (of different acidities), small amounts of finely divided red, red-orange, or orange crayons were added. These mixtures were shaken for one hour and then examined for parared. No parared was detected.

It was first assumed that the presence of primary aromatic amines would indicate degradation of the parared dye in the gastric fluid. The reaction for primary aromatic amine was positive in all instances. However, untreated gastric fluid also gave a positive reaction.

3. A small dog, weighing 9 kg., was fed approximately 3 Gm. of the orange crayon by stomach tube. The dog did not develop any signs of poisoning. The blood, which was free of methemoglobin before feeding the crayon, did not show methemoglobin either 2½ hours or 24 hours after feeding.

Another dog, weighing 15 kg., was fed approximately 4.5 Gm. of the orange crayon by stomach tube. The negative findings corresponded to the findings in the first dog.

A third dog, weighing 34 kg., received 6 Gm. of orange crayon through a stomach fistula. Likewise, in this experiment no clinical or blood changes were observed.

Urinalyses are shown in Table IV. There was no evidence of para-aminophenol.

TABLE IV. PARA-AMINOPHENOL IN URINE

REAGENT	COLOR REACTION	CONTROL (URINE AND P-AMINOPHENOL)
Dilute $NaNO_2$	Pale yellow	Pale yellow
β-naphthol	Negative	Positive (green-brown)
5% phenol + NaClO	Negative	Positive (deep blue)
H_2S Water	Negative (greenish)	Positive (deep purple)

All dogs received the crayon on an empty stomach.

In order to ascertain the toxic effect of para-nitraniline in our dogs, dog 1 was fed approximately 0.015 Gm. paranitraniline by stomach tube. The dog showed slight but definite signs of poisoning; methemoglobin was not found.

Our findings confirm that orange and red-orange crayons contain parared, the basic constituent of which is paranitraniline. However, the dogs did not show any signs of poisoning after ingestion of appreciable amounts of orange

crayon. This is in accordance with the general consensus that the finished dye is insoluble and harmless.

On the other hand, the case of poisoning herein reported was undoubtedly due to paranitraniline. We are, at present, still unable to explain the mechanism of the poisoning in this case. The finished dye does not contain an excess of free paranitraniline.

DISCUSSION AND CONCLUSIONS

The clinical and biochemical findings in our case are identical with those described in acute, and especially in acute industrial paranitraniline poisoning.[8-12]

The crayons ingested by the child were evidently the source of the poisoning, since she did not have access to any other material that could have caused the symptoms observed. The red-orange crayon used by the child was found to contain parared, an organic pigment made by coupling diazotized paranitraniline with beta-naphthol.

Poisoning in industry has been due to paranitraniline itself. The developed dye (parared) as contained in wax crayons, is supposed to be insoluble. In our case, para-aminophenol, an intermediate oxidation product of aniline in the body, was found in the urine. The positive amine reaction in the gastric fluid is not, however, of specific significance, since we ascertained later that normal gastric fluid gives this reaction.

Poisoning through ingestion of paranitraniline is "exceptional," according to the literature.[11] The fact that our patient had not taken food or liquid for at least twelve hours preceding the ingestion of the crayons was probably important. In Lehmann's[13] experiments, cats and rabbits with full stomachs tolerated much more paranitraniline than animals with empty stomachs.

SUMMARY

Severe poisoning of a 3-year-old child through ingestion of wax crayons was described.

Clinical and biochemical findings were identical with those reported in industrial paranitraniline poisoning.

A piece of red-orange wax crayon recovered from the vomitus was examined chemically. It contained parared, an organic pigment made by coupling diazotized paranitraniline with beta-naphthol.

Conjugated para-aminophenol, an intermediate oxidation product of aniline in the body, was found in the urine.

Parared is used also in painting toys.

Animal experiments were conducted by one of us (H. B). to obtain additional information about the nature and mechanism of this type of poisoning.

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DOUBLE AORTIC ARCH

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ANOMALIES of the aortic arch and its main branches were long considered interesting incidental post-mortem findings, clinically insignificant and of interest mainly for the light they shed on the normal development of the human arterial system. In reporting a case of double aortic arch found in a dissecting room specimen, a male aged 67, Lockhart (1929)[1] used the following phrase which was typical of the general attitude: "The whole interest of such a specimen lies in the fact that it stands as a milestone of striking and historic architecture upon the byways of development."

In 1837, Von Siebold[2] wrote of an infant who died at the age of 10 days, having had respiratory stridor, dyspnea, and cyanosis since birth. In addition to an interauricular septal defect and complete transposition of the great vessels, the infant had a complete double aortic arch which Von Siebold believed to have been the cause of the infant's marked stridor and dyspnea while feeding.

Buschendorff (1917),[3] Schleussing (1925),[4] and Ewald (1926)[5] each described one case, and in each, the symptoms and signs were almost identical. Since early infancy each patient had suffered from respiratory stridor, paroxysmal dyspnea, particularly during feeding, and ultimate death from asphyxia, despite x-ray treatment of a suspected enlarged thymus. Death in these infants occurred at the ages of 6 weeks, one month, and 5 months, respectively. Each was found post mortem to have been suffering from tracheal and esophageal compression by a double aortic arch.

Harris and Whitney (1927)[6] reported the case of a boy who had cyanosis and inspiratory stridor since birth and who died at the age of 19 months. In addition to an interventricular septal defect and complete transposition of the great vessels, a double aortic arch which was believed to be constricting the trachea was found at autopsy. Hermann (1928)[7] performed an autopsy on a 6-month-old infant who had suffered from cough, stridor, intermittent cyanosis, and head retraction since 2 months of age and found a double aortic arch encircling and constricting both the trachea and esophagus.

In 1933, Snelling and Erb[8] had a similar patient who had inspiratory stridor and respiratory difficulty during feedings since birth. Cyanotic attacks began at the age of 3½ months, at which time a barium swallow showed posterior compression of the esophagus at the level of the third and fourth dorsal vertebrae. The authors had a personal report from Blackfan[9] of a 5-month-old infant who died with similar symptoms and signs, and was found post mortem to have a right aortic arch with a persistent left ligamentum arteriosum causing tracheal and esophageal obstruction. Because of the similarity of the cases, a diagnosis of right aortic arch was made by Snelling and Erb in their case. However, when the infant died at the age of 4 months, the cause of respiratory dis-

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tress was found to be a constricting vascular ring made up of a double aortic arch. In these cases the symptoms and signs were identical and similarly produced, but in the first the constricting vascular ring was formed by the right aortic arch and left ligamentum arteriosum, while in the second it was formed by a double aortic arch.

Arkin (1926)[10] made a diagnosis of double aortic arch in six living adults, and in two cases the diagnosis was later confirmed at autopsy. These diagnoses were roentgenologic and accidental, in the sense that they were made in persons who were under investigation for symptoms unrelated to their vascular abnormalities.

Increasing cognizance was given to the syndrome produced by constricting vascular ring in infants, i.e., stridor, respiratory difficulty particularly while feeding, cyanotic attacks, and frequent head retraction. However, it remained as an academic diagnostic possibility, since no treatment was considered possible. Jex-Blake (1926)[11] described a puppy who suffered from increasing stridor and dysphagia. At autopsy the trachea and esophagus were found to be constricted by a right aortic arch and the ligamentum arteriosum attaching it to the left pulmonary artery. It was suggested by the author that surgical therapy in such a case would have been simple had the correct diagnosis been made. Not until 1939 was any further written suggestion made of therapy in such cases. Wolman (1939)[12] reported the case of a 4-month-old infant who died with the syndrome which we have outlined as typical of a constricting vascular ring. These symptoms were not relieved by irradiation of the thymus and no evidence of a mediastinal tumor was found. Autopsy revealed tracheal and esophageal compression by a double aortic arch. Wolman reviewed the previous reports of this syndrome and suggested that such patients would be susceptible to surgical treatment if an antemortem diagnosis could be made.

Schall and Johnson (1940)[13] reported the case of a 6-month-old infant who had the typical syndrome for four months before death. Bronchoscopy showed a constriction of the trachea at the carina, and dyspnea was relieved during bronchoscopy. Surgery was not attempted, and at autopsy a double aortic arch was found to be the constricting agent.

Maude Abbott (1931),[14] in a study of 1,000 cases of congenital heart disease, described five cases of double aortic arch, in two of which there were symptoms. Blackford and associates (1932)[15] wrote a complete discussion of congenital aortic anomalies, considering their embryologic etiology in particular. Blincoe and associates (1936)[16] compiled an even more complete bibliography of these conditions, prompted by their finding of an unsuspected double aortic arch in a post-mortem examination of an adult. Of forty cases of double aortic arch in the literature, they found that seven were in fetuses or infants who died in early life, twelve were accidental findings in adults, seven were poorly described, and twelve were asymptomatic adults, but in these there was a persistent right aortic arch and vestigial cords only of the left arch. Herbut (1943)[17] reviewed the congenital aortic anomalies found in 5,800 consecutive autopsies. He found no cases of tracheal or esophageal compression by right aortic arch with persistent left ligamentum arteriosum nor of symptoms from an anomalous right

subclavian artery. Of the two cases of double aortic arch, one was in an asymptomatic adult and the other was a 2½-month-old infant who had stridor, dyspnea, and cyanosis from birth.

In most of these reports of double aortic arch, the right (posterior) arch which runs behind the esophagus is described as being larger than the left (anterior) arch and running at a slightly higher level. In both of Arkin's cases there was a partial atresia of the left arch, which he incorrectly assumed to be the rule when a double aortic arch persisted. In the forty cases reviewed by Blincoe and associates,[16] only two patients were found to have the left arch larger than the right. In the single case reported by Schall and Johnson[13] the two arches were identical.

In all those reports in which the aortic branches are mentioned, each aortic arch is described as giving rise separately to its appropriate common carotid and subclavian arteries. In fact, the right (posterior) arch has two branches, the right common carotid and subclavian arteries; similarly, the left common carotid and subclavian arteries arise from the left aortic arch. In a few cases the right arch gives rise to a small vertebral artery, and in a few a patent ductus arteriosus or ligamentum arteriosum joins the left arch. In none of these cases is a right or left innominate artery described. Herbut[17] states categorically, "There is no innominate artery."

It may seem that undue emphasis is being laid upon the typical syndrome produced by a constricting vascular ring and the uniformity of the anatomic findings in the majority of cases. The condition of double aortic arch is of particular interest now, however, inasmuch as surgical treatment of it has been initiated recently. Gross (1945)[18] published a report of the first case of constricting vascular ring correctly diagnosed and treated. The patient was first seen at 4 months of age with the complaint of wheezing since birth. Thymic irradiation had no effect on the symptoms. He was seen intermittently during the rest of the first year of his life, and had acute febrile exacerbations of dyspnea and stridor. When he was about one year old, investigations were carried out in an attempt to find the cause of these episodes of respiratory difficulty. Roentgen studies of the esophagus after a barium swallow revealed a posterior indentation and forward displacement of the esophagus at the level of the third to fourth thoracic vertebrae. Similarly, studies of the trachea and bronchi after lipiodol instillation showed a constriction of the trachea just above the carina, at the same level as the compression of the esophagus. A diagnosis of constricting vascular ring was made and an operation was performed. At operation a double aortic arch was found and the smaller (left) anterior arch was divided. The ligamentum arteriosum, which joined the anterior arch, was also divided. The right arch was described as giving rise to a right innominate artery. The infant was relieved of his symptoms and made an uneventful recovery. Faber (1945)[19] has described two patients aged 2½ months and 2½ years, who both had persistent stridor and were shown radiologically to have a right aortic arch. It is probable that both these children had a constricting vascular ring produced by the persistence of a left ligamentum arteriosum.

Such cases should prove even more amenable to surgical treatment than those of double aortic arch. I can find no record of symptoms being produced by a partially atretic left arch with a persistent right (posterior) arch, but there is no reason why this should not occur. During the past ten years there have been, in this hospital, autopsies on ninety-five children under 13 years of age who had congenital cardiovascular anomalies. Of these, four had a complete double aortic arch. There were no cases of other forms of constricting vascular ring.

Summaries of the case records of the four children with double aortic arches follow. In the first child, there were no signs or symptoms produced by the vascular ring. The case is being presented for its anatomic interest. The other three infants had a constricting vascular ring and are therefore of both clinical and anatomic interest.

CASE REPORTS

CASE 1.—D. B., a white female infant, was born at full term weighing 8 pounds, 9 ounces, after a normal pregnancy and labor. The infant was breast fed for one year and developed normally with no respiratory symptoms and no illness. The family history was noncontributory. At the age of 20 months a severe diarrhea developed, and two days after the onset, on Sept. 6, 1940, the patient was admitted to the Children's Memorial Hospital. The child was found to be in a serious condition, toxic, and dehydrated. Diarrhea was persistent, accompanied by vomiting and extreme toxemia. The stool culture was positive for *Shigella paradysenteriae*. Despite intravenous fluids and daily blood transfusions from Sept. 11, 1940, the child's condition did not improve. On September 16, increasing abdominal distension was noted with dullness in the flanks, and a diagnosis of peritonitis was made. Intravenous sulfanilamide was given for twenty-four hours, but was discontinued because the white count fell to 1,600. The child died on September 20, after many rectal hemorrhages and the development of pulmonary congestion. At no time was there any stridor or cyanosis nor other evidence of respiratory obstruction. The clinical diagnosis was: (1) flexner dysentery, (2) peritonitis, and (3) bronchopneumonia.

Necropsy Findings.—The clinical impression was confirmed by the findings post mortem. There was an acute inflammation of the mucosa of almost the entire gastrointestinal tract, with gangrene of the terminal ileum and the colon. The gangrene extended through the entire wall of the transverse colon and perforation had occurred in its midportion, leading to a purulent peritonitis from which *Shigella paradysenteriae* was cultured. In addition, there was generalized pulmonary congestion, with bronchopneumonia of the right upper lobe.

An unexpected finding was an anomaly of the aortic arch. The heart was of normal size and structure, the only abnormality being a small hemorrhage into the myocardium of the left ventricle. With the exception of the aortic arch and its branches, there were no vascular anomalies. Shortly after its origin, the aorta divided into an anterior and posterior arch, which encircled the trachea and esophagus and joined to form the descending aorta. Each arch gave rise separately to its respective common carotid and subclavian arteries. There was no innominate artery. A large patent ductus arteriosus joined the left arch. There is no record of the relative levels of the two arches nor of their size. The pathologic diagnosis was: (1) bacillary dysentery (Flexner), (2) acute purulent peritonitis, (3) double aortic arch, and (4) patent ductus arteriosus.

CASE 2.—D. M., a 4-month-old white female infant, was first seen in The Children's Memorial Hospital Nov. 21, 1942, and was admitted on that day. The infant was born at full term weighing 8 pounds, 2 ounces after a normal pregnancy and labor. Shortly after birth, she had three "blue spells," but had none since. She was a breast-fed baby and developed normally except that she had very noisy respirations, particularly when awake. The family history was noncontributory.

Five days before admission to the hospital, the infant developed a cough, fever, and listlessness. These symptoms got worse and when first seen she was in a state of collapse.

The temperature was subnormal, the extremities were cold, and respirations were rapid. There was marked perioral cyanosis. No abnormal chest findings were noted, although stridor was marked, and diagnosis was deferred. X-ray of the chest showed collapse of the upper and lower lobes of the right lung, and air seen anterior to the heart was interpreted as a pneumomediastinum. However, exploratory aspiration of the anterior mediastinum failed to yield any air. On the day of admission, a bronchoscopic examination was performed and external compression of the left main bronchus was noted, but the etiology was obscure.

The infant was kept in an oxygen tent where her color was good but her respirations remained noisy. The chest was partly fixed in the inspiratory position and there was emphysema of the left lung. Fluids were given intravenously, as were 0.5 Gm. sodium sulfathiazole every six hours and ¾ grain aminophylline three times daily. Attempts at oral feeding produced marked respiratory distress with cyanosis. On November 23, 50,000 units of antipneumococcus serum type 14 was given because culture of the bronchoscopic aspirations yielded pneumococcus type 14. On November 24, 125 c.c. of whole blood were given intravenously. The white count ranged from 29,000 to 36,000, but the temperature remained normal until November 25, when it rose sharply and death ensued. The clinical impression was: (1) acute laryngotracheobronchitis, (2) atelectasis of the right upper and lower lobes, and (3) aspiration pneumonia.

Necropsy Findings.—The abnormal findings at post mortem on this well-developed, 14½ pound female infant were limited to the vascular and respiratory systems. The heart was of normal size and structure. The great vessels arose normally but, shortly after its origin, the aorta divided into two branches which encircled and compressed the trachea and esophagus before uniting to form the descending aorta. The right (posterior) arch gave rise separately to the right common carotid and subclavian arteries. The left (anterior) arch also had two branches, the left common carotid and subclavian arteries, and was joined by the left ligamentum arteriosum. The measurements and relative levels of the two arches were not recorded. No other vascular anomalies were noted.

The trachea was collapsed just above the carina and there was atelectasis of the right upper and lower and left lower lobes of the lungs. In the atelectatic lobes there was an early bronchopneumonia. The left upper and right middle lobes were emphysematous. The pathologic diagnosis was: (1) double aortic arch, (2) tracheal compression with atelectasis of three lobes and emphysema of the other two, and (3) early bronchopneumonia.

CASE 3.—M. W., a white female infant, weighed 6 pounds, 12½ ounces, when born at full term after a normal pregnancy and labor. The family history was noncontributory.

Shortly after birth she had two attacks of cyanosis, which did not recur, but she had persistently noisy breathing. A diagnosis of enlarged thymus was made, but no x-ray therapy was given. From birth the infant was a feeding problem. She had many formula changes and regurgitated most of them. She gained slowly but had no illness until two weeks before she was admitted to the Children's Memorial Hospital, when she developed a cough, fever, and irritability, respiratory distress, and diarrhea. She was brought to the hospital on Feb. 21, 1943, in an apparently moribund state, with a temperature of 106° F., deep cyanosis, and slow, gasping, noisy respirations. There was suppression of the breath sounds on the right side, with a pause after inspiration. The infant was placed in an oxygen tent and was given Coramine and adrenalin at once, followed by intravenous fluids and 3.85 grains of sulfathiazole every four hours orally. An x-ray of the chest showed atelectasis of the right upper lobe and emphysema of the left lower lobe which was thought to be obstructive, but bronchoscopy was not done because of the infant's serious condition. One hundred cubic centimeters of whole blood were given intravenously on Feb. 22, but a bloody diarrhea and bleeding from the nose and mouth developed. The infant died on the third hospital day. The clinical impression was (1) right bronchopneumonia and (2) diarrhea.

Necropsy Findings.—Abnormal findings were limited to the vascular and respiratory systems in this infant also, but the baby was not so well nourished as the previous one. The heart was of normal size and structure, with the greatest vessels arising in the usual way.

However, the aorta divided into two arches, the larger running behind the esophagus and the smaller crossing in front of the trachea before they joined to form the descending aorta. The trachea and esophagus were constricted by this vascular ring. The smaller, left arch was joined by a fine patent ductus arteriosus and gave rise to the left common carotid and subclavian arteries. The two branches of the right arch were the right common carotid and subclavian arteries. There were no other vascular anomalies.

The upper lobe of the right lung was atelectatic, and the middle lobe was congested. The left lung was emphysematous. The pathologic diagnosis was: (1) double aortic arch, (2) atelectasis of right upper lobe, (3) congestion of right middle lobe, and (4) emphysema of left lung. The last of the four cases we are reporting is particularly illuminating.

CASE 4.—D. Z., a white male infant, was born at full term after a normal labor with a birth weight of 8 pounds. His mother had been diabetic since childhood, but the pregnancy, her second, had been uneventful. Her first pregnancy ended after seven months, and the male infant died, at the age of 3 months, of congenital heart disease. Otherwise, the family history was noncontributory.

The baby was in oxygen for some time after birth but went home at 3 weeks of age. He was well until 5 weeks of age, when his mother first noticed noisy and difficult breathing which was worse while feeding or lying. The stridor became worse, and attacks of cyanosis became so frequent that the baby was hospitalized at the age of 7 weeks. A diagnosis of aspiration pneumonia was made, and the baby remained in the hospital until he was transferred to the Children's Memorial Hospital on June 29, 1946, at the age of 4 months.

On admission, the infant weighed 15 pounds, 2 ounces. He was well developed and well nourished, having marked inspiratory stridor with substernal and supraclavicular retractions, but no persistent cyanosis. He was at first kept in an oxygen tent, however, because when they did occur, his attacks of cyanosis were alarmingly severe.

Roentgenograms of the chest showed no mediastinal tumor but a moderate upper mediastinal widening which was interpreted as an enlargement of the thymus but which did not diminish after thymic irradiation.

On June 30, a bronchoscopic examination was made and a high-grade compression stenosis of the trachea, at the carina, and of both main bronchi was seen.

On July 3, x-ray study of the esophagus after a barium swallow showed no abnormality, but a tentative diagnosis of constricting vascular ring had been made, and on July 12 another bronchoscopy was done. The same compression was seen; the stenosis was dilatable, but collapse recurred immediately on withdrawing the bronchoscope. The infant had such severe respiratory distress that an examination of the tracheobronchial tree after lipiodol instillation was not considered safe.

The infant continued to have one or more severe attacks of cyanosis each day, usually during or just after feeds, but between these episodes he was comfortable out of oxygen. During each one of these periods of cyanosis it seemed as though death was imminent, but aspiration and oxygen relieved him.

On July 25, lipiodol was given by mouth, and on fluoroscopic examination the material was seen to hesitate at the level of the third intercostal space, at which level posterior esophageal compression was noted. A diagnosis of constricting vascular ring was made, and, on July 27, an exploratory thoracotomy was performed.

*Operative Note.**—Under cyclopropane anesthesia, the left pleural cavity was opened anteriorly through the third interspace. The third and second ribs were cut at the sternal margin. Adequate exposure was obtained with a rib-spreader. The mediastinal structures were exposed through a longitudinal incision in the mediastinal pleura lateral to and parallel with the phrenic nerve. The ductus arteriosus was found to be obliterated. The arch of the aorta appeared normal in size and position. The innominate left common carotid and left sub-

*The Surgeon was Willis J. Potts, M.D.

clavian arteries apparently arose from the aorta in their usual normal positions. There was no evidence of a vascular ring or any other abnormality. The mediastinal pleura was repaired and the chest closed. The ribs were apposed with three catgut sutures encircling adjoining ribs, the second and third ribs were sutured to their sternal margins and the muscles sutured with catgut. As the last suture was put in the muscles of the chest wall, negative suction was made on a catheter in the pleural cavity to reexpand the lung. The skin was closed with silk. The child left the operating room in good condition.

After operation the infant did well and remained afebrile. There was good pulmonary aeration and no cyanosis. However, on the evening of the third postoperative day, he had a sudden, particularly severe attack of cyanosis in which he died.

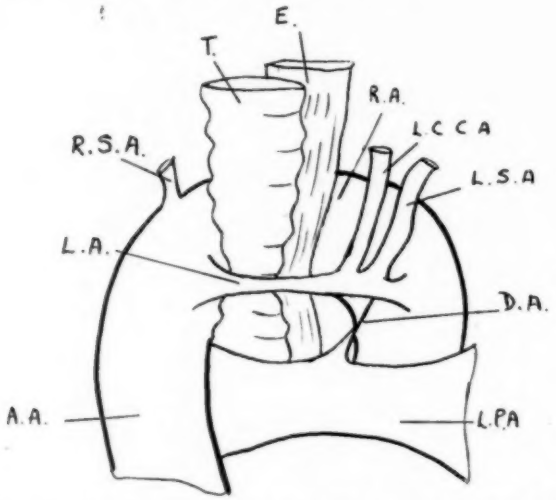

Fig. 1.—Composite diagram illustrating the usual anatomy of double aortic arch, anterior view.
A.A., ascending aorta.
R.A., right (posterior) aortic arch.
L.A., left (anterior) aortic arch.
R.S.A., right subclavian artery.
L.C.C.A., left common carotid artery.
R.C.C.A., right common carotid artery.
L.S.A., left subclavian artery.
D.A., ligamentum arteriosum or ductus arteriosus.
L.P.A., left pulmonary artery.
T., trachea.
E., esophagus.
R.V., right vertebral artery.

Necropsy Findings.—Once again the abnormal findings were limited to the vascular and respiratory systems. The infant was well nourished and well developed. The heart was normal in all respects, as was the vascular system with the exception of the aorta. The ascending aorta divided into two branches, which encircled and constricted the trachea and esophagus, and united to form the descending aorta. The left arch was the normal size of the aorta and lay slightly higher than the smaller posterior (right) arch, obscuring it from the anterior aspect. Each arch had two branches, the respective common carotid and subclavian arteries. There was no ductus arteriosus and no innominate artery, though the latter was simulated by the origin of the smaller, right arch. The lungs showed generalized congestion, with no atelectasis or infection. Pathologic diagnosis was (1) constricting double aortic arch and (2) asphyxia.

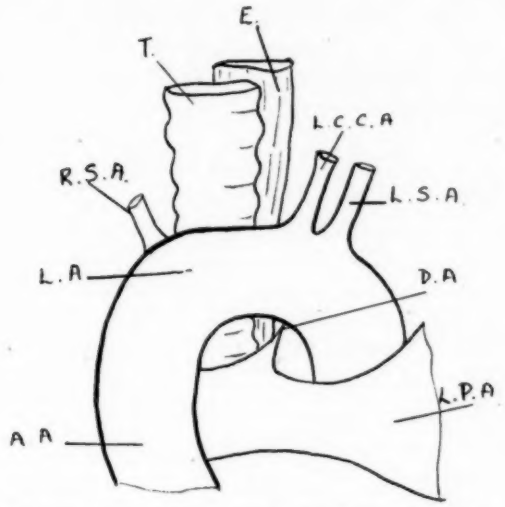

Fig. 2.—Anterior view of the double aortic arch in Case 4.

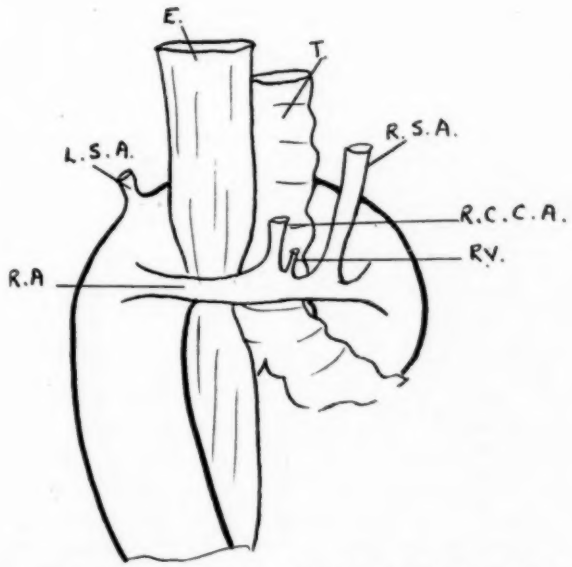

Fig. 3.—Posterior view of the double aortic arch in Case 4.

The particular importance of the last case is to emphasize that on rare occasions the usual anatomic structure of a double aortic arch is not found. The anterior arch may be both larger and higher than the posterior arch, obscuring the latter from the anterior aspect. This was the condition found in our last case. Also, with the exception of the case described by Gross,[18] I can find no record of a double aortic arch in which there was either a right or left innominate artery. In this case, what appeared to be the right innominate artery was actually the right subclavian artery, which arose from the posterior arch immediately after the aorta bifurcated.

It should be clear from the foregoing discussion that constricting vascular ring is not common, neither is it excessively rare. In particular, now that surgical therapy has been proved possible, the diagnosis should be borne in mind in cases of respiratory stridor in early life in which there are no laryngeal or tracheal abnormalities, no mediastinal tumor and no symptomatic response to irradiation of the thymus. The typical syndrome of constricting vascular ring has been fully re-emphasized in this paper, and the findings which corroborate the diagnosis are clearly set forth by Gross (1945).[18] Double aortic arch is by far the most common aortic anomaly to produce the typical syndrome, but it is important to realize that an identical syndrome can be produced by other anatomic abnormalities. A right aortic arch with persistent left ductus arteriosus or ligamentum arteriosum can form the constricting ring. Constriction of the esophagus, and sometimes of the trachea, is sometimes caused by the right subclavian arising from the descending aorta and running behind the esophagus. Similarly, the left subclavian may arise from a retroesophageal diverticulum of a right aortic arch and thus cause esophageal compression. These conditions are all fully considered by Gross (1946)[20] in an article dealing with the surgical approach to such abnormalities. In this paper we have considered only double aortic arch as a cause of constricting vascular ring because it is most common and because there have been three cases in this hospital in the last ten years, while there has been no case with symptoms produced by the other aortic anomalies encountered.

SUMMARY

A review is made of eleven reported cases of double aortic arch in infancy, with descriptions of four other instances occurring in The Children's Memorial Hospital in the past ten years. One of these four patients had no respiratory symptoms, but the other three and the ten previously reported each had the typical syndrome of respiratory stridor since early infancy, made worse by feeding or lying prone, attacks of cyanosis, and susceptibility to pulmonary infections. Many were treated for an enlarged thymus without success.

In view of the surgical therapy now possible, emphasis is laid on the anatomy of double aortic arches. In all except one of the thirteen cases in infants, the left (anterior) arch was smaller and lower than the right (posterior) arch. In only one case was an innominate artery described; in all the others each arch gave rise separately to its respective common carotid and subclavian arteries.

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ACUTE MENINGOCOCCEMIA

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ALTHOUGH there is general appreciation of the fact that a transient bacteremia is often a concomitant finding in meningococcic infections, the extreme propensity of the meningococcus toward invasion of the cerebrospinal meninges has caused many physicians to lose sight of the fact that acute meningococcic septicemia without meningitis is rather frequently encountered. Such an infection was first described by Soloman[1] in 1902. Since that time there have been numerous reports describing one or more cases, and in some of the more recent general discussions of meningococcic infections[2-7] the clinical picture of acute meningococcic septicemia has been noted. There are several recent discussions of meningococcemia without meningitis, in which a number of cases have been discussed.[8-12]

In the period between Oct. 20, 1941, and Aug. 31, 1946, there have been 296 patients with meningococcic infections treated in the Gallinger Municipal Hospital. The general plan of treatment and the results obtained in patients with meningitis have been reported elsewhere.[13-15] The purpose of the present paper is to describe the clinical syndrome presented by the sixteen patients treated during this period because of a meningococcemia without meningitis.

The first of these patients was admitted to the hospital Oct. 25, 1941, the last on Aug. 3, 1946. Four patients were admitted during 1943, three each in 1944 and 1945, and five in 1946. The youngest patient was 2 months old, the oldest, 54 years. There were four patients who were less than 1 year, two from 1 to 9, seven from 10 to 19, and three over 20 years of age. There were six female and ten male, eight Negro and eight white patients.

The clinical picture presented by these sixteen patients followed one of two patterns. Fourteen patients had mild or moderately severe illness, and presented a similar picture; two had a severe fulminating infection. (Table I.) These two groups will be discussed separately.

MILD OR MODERATELY SEVERE ILLNESS (CASES 1 TO 14)

Clinical Features.—The duration of illness at the time of admission varied from less than one to six days. Six patients entered the hospital after being ill only one day and eight came in after being ill from two to six days. The history revealed that headache, fever, vomiting, and joint pains were almost uniformly present. Headache, which was complained of by nine of eleven patients who were old enough to identify the symptom, was severe and constant, but not as excruciating as that which is usually present with meningitis. The three infants who were too young to complain of headache were extremely irritable. Ten

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of the fourteen patients had vomited. This was usually nonprojectile. Eight patients complained of vague, generalized, joint pains, and one 50-year-old man had severe purulent arthritis of his wrists and the joints of one foot.

Fever was noted in the history of thirteen patients. It was present at the time of hospitalization of all these patients, ranging from 101.0 to 105° F. The maximum recorded temperature was 104° F. or over in eight patients, between 102 and 104° F. in five, and 101° F. in one. It lasted from eight hours to eight days, with seven patients being afebrile within twenty-four hours, and seven patients running a fever for between two and eight days.

A skin rash was recognized prior to admission by only six patients, but was recorded in the physical examination of all fourteen patients. The type of rash found in patients with meningococcemia is of considerable importance, and should be sought for with great care. It has been described by many recent observers. In nine of our patients the major rash was a discrete, widely scattered, maculopapular eruption that showed maximal concentration on the trunk or on the extremities with approximately equal frequency. It was usually present also on the palms and soles. The individual lesions varied from 1 to 5 mm. in diameter, were slightly raised, and usually faded on pressure. They were quite comparable in appearance with the rose spots seen in typhoid fever, but were usually more numerous. In only one patient were there larger, more indurated skin lesions which did not fade on pressure and which resembled the lesions which have often been observed in patients with chronic meningococcemia.[16-17] Petechiae were present as an associated finding in two of these nine patients with a maculopapular rash. In both they were small and widely scattered. In one 10-year-old girl they were found after the maculopapular rash had faded completely. Five patients showed a petechial and purpuric rash of the type more generally seen in patients with meningococcic meningitis, without other cutaneous manifestations.

Other than the fever and skin rash, the most frequently noted physical finding was a generalized arthralgia or arthritis. This was present in eight patients. One patient demonstrated a slight swelling of his wrists and ankles, and six patients complained only of stiffness of the joints and pain on motion. This symptom was very transitory and disappeared rapidly. The patient with a purulent arthritis from which meningococci were recovered had severe symptoms with residual stiffness of the joints at the time of his discharge.

Laboratory Data.—The pertinent laboratory findings obtained in these patients are summarized in Table II. The meningococcus (*Neisseria intracellularis*) was recovered from cultured blood in thirteen of the fourteen patients. The organism was typed in eight instances, in five of which it was found to belong to Group I, in two to Group II, and in one to Group IIa. Satisfactory typing was not obtained in five instances. The diagnosis in the disease in the remaining patient was made by the demonstration of serum agglutinins against the Group I meningococcus. Seven cultures of his blood were sterile.

The hemogram showed very slight abnormalities in the twelve patients for whom it was recorded during the most acute phase of the illness. The white

TABLE I. CLINICAL FEATURES OF SIXTEEN PATIENTS WITH ACUTE MENINGOCOCCEMIA

					SYMPTOMS					RASH			TEMPERATURE	
CASE	SEX	RACE	AGE (YR.)	DURATION OF ILLNESS AT ADMISSION (DAYS)	HEADACHE	VOMITING	ARTHRALGIA	FEVER	OTHER SYMPTOMS	MACULOPAPULAR	PETECHIAL	DURATION (DAYS)	MAXIMUM (° F.)	DURATION (HOURS)
1	M	N	9	4	+	+	+	+	Sore throat	Extremities	0	N.R.*	102.6	8
2	F	N	10	1	+	+	0	+	Stiff neck, rash	Generalized	Few	3	104.0	12
3	M	W	11	6	+	+	+	0	Abdominal pain	Trunk	0	4	104.8	72
4	F	N	7	1	+	+	+	+	-	Trunk	0	N.R.	106.0	20
5	F	N	27	1	+	0	+	+	Chills, stiff neck	0	Generalized	N.R.	104.6	104
6	M	N	13	1	+	+	0	+	Chill	Trunk	0	N.R.	105.2	8
7	F	N	7/12	5	?	+	0	+	Irritability	Extremities	Few (later)	2	102.0	16
8	F	W	8/12	5	?	+	+	+	Irritability	0	Extremities	5	104.0	72
9	M	N	16	4	+	0	+	+	Lethargy	Generalized	0	8	104.6	192
10	M	N	2/12	4	?	+	0	+	Irritability	Face and legs	0	N.R.	102.2	24
11	M	W	16	2	0	+	+	+	-	Generalized	0	4	103.0	32
12	F	W	54	1	+	0	+	+	Dizziness	0	Few, sclerae and arms	2	104.0	48
13	M	W	10	1	+	+	0	+	Convulsion	0	Generalized (few)	4	101.0	16
14	M	W	50	5	0	0	++	+	Purulent arthritis	0	Generalized	6	102.0	96
15	M	W	10/12	1	?	+	+	+	Rash	0	Generalized		108.0	Died
16	M	W	18	N.R.	N.R.	+	+	+	Shock	0	Generalized	N.R.	103.2	108

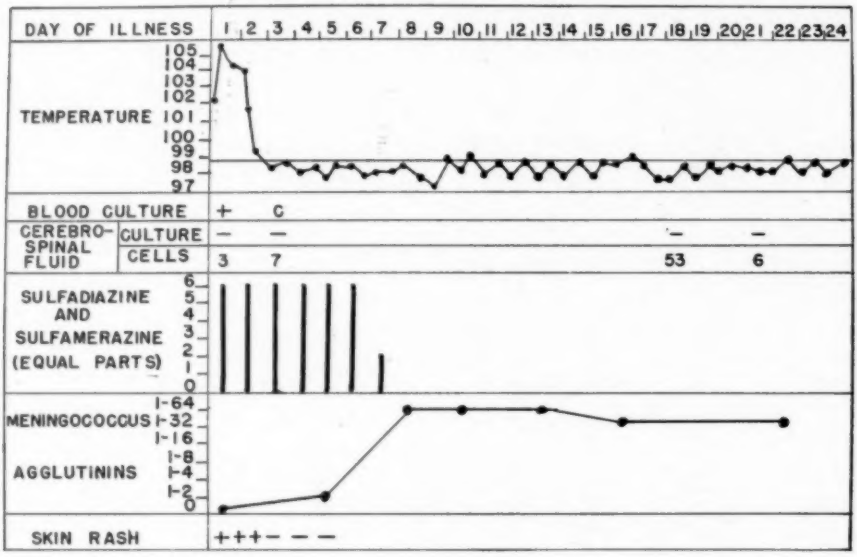
*N.R. = no record.

TABLE II. LABORATORY DATA FOUND AND TREATMENT EMPLOYED IN SIXTEEN PATIENTS WITH ACUTE MENINGOCOCCEMIA

CASE	AGE (YR.)	BLOOD				CEREBROSPINAL FLUID		TREATMENT
		W.B.C.	AGGLUTINATION DAY	AGGLUTINATION TITER	BLOOD CULTURE MENINGOCOCCI	RELATION TO BLOOD CULTURE	FINDINGS	
1	9	N.R.*	N.R.	-	Group I	Not done	-	Supportive
2	10	N.R.	N.R.	-	Group I	30 minutes before	Normal	Sulfadiazine
3	11	7,060	N.R.	-	No group	At time of contaminated culture, 2 days before positive culture	Normal	Supportive
4	7	11,500	16	1:64	Group I	One hour before	Normal	Supportive
5	27	11,250	12	1:16	Group I	1½ hr. before, 1 and 2 days after	Normal	Sulfadiazine and sulfamerazine
6	13	10,500	7 & 12	1:64	No group	Same time and 2 and 19 days after 16 days after	Normal 53 cells	Sulfadiazine and sulfamerazine
7	7/12	8,600	N.R.	-	No group	5 days after	Normal	Sulfadiazine and sulfamerazine
8	8/12	7,600	N.R.	-	No group	Not done	-	Sulfapyridine
9	16	4,300	29	1:128	Negative	3 occasions during fever	Normal	Sulfadiazine
10	2/12	12,050	N.R.	-	Group II	Not done	-	Supportive
11	16	12,050	N.R.	-	Group II	Between 2 positive cultures	Normal	Sulfadiazine 24 hours after entry (day after spinal tap)
12	54	N.R.	N.R.	-	Group I	Same time and 1 day after	Normal	Sulfadiazine day after entry (day after spinal tap)
13	10	4,700	N.R.	-	No group	Same time	Normal	Sulfadiazine and sulfamerazine
14	50	6,500	N.R.	-	Group IIa	Same time	Normal	Sulfadiazine and sulfamerazine
15	10/12	25,000	N.R.	-	No group	Same time	Normal	Penicillin, sulfadiazine, and sulfamerazine, plasma
16	18	10,600 38,150	N.R.	-	Group I	Same time	Normal	Sulfadiazine, and sulfamerazine, plasma, penicillin, adrenal cortex extract

*N.R. = no record.

blood cell count ranged from 4,300 to 12,050 per cubic millimeter in these twelve patients and the differential count showed from 58 to 90 per cent cells of the polymorphonuclear series. In the patients with high granulocyte counts there was a moderate shift to the left in the Schilling index.


DAY OF ILLNESS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TEMPERATURE
105 104 103 102 101 100 99 98 97
BLOOD CULTURE
+ C
CEREBRO-SPINAL FLUID
CULTURE
CELLS
3 7 53 6
SULFADIAZINE AND SULFAMERAZINE (EQUAL PARTS)
6 5 4 3 2 1 0
MENINGOCOCCUS AGGLUTININS
1-64 1-32 1-16 1-8 1-4 1-2 0
SKIN RASH
+++ − −

C= CONTAMINATED

Fig. 1.—Clinical course, treatment, and significant laboratory findings in a typical case of acute meningococcemia without meningitis (Case 6).

Blood serum agglutinins against meningococci were studied in four patients. All gave positive agglutinations, with titers similar to those reported for patients with meningococcic meningitis.[18] A graph of a typical agglutinin response as it occurred in Case 6 is shown in Fig. 1, together with the clinical picture. A single titer positive in a dilution of 1:128 was obtained on the twenty-ninth day of illness in the patient who showed skin lesions similar to those found in chronic meningococcemia. Titers positive to 1:64 were obtained on the seventh to twelfth days and the fourteenth day respectively in two patients, and 1:16 on the twelfth day in the fourth patient studied. The development of antibodies in patients with meningococcemia has been demonstrated also by Silverthorne[19] and Daniels.[2]

The spinal fluid was examined in one or more occasions in eleven patients. It was entirely within normal limits on each occasion, with the single exception of one patient (Case 6) who showed a pleocytosis with fifty-three cells per cubic millimeter on one occasion sixteen days after entry. Specimens of spinal fluid from this patient examined at the time of admission and two and nineteen days after entry were entirely normal, and since the patient was entirely asymptomatic it is probable that the pleocytosis noted was due to an error in the counting.

Treatment.—The only specific treatment used in this group of patients was the administration of one of the sulfonamides to ten. The other four patients responded to supportive care alone. Although they had maximal temperatures of 102.6, 104.8, and 106° F., they became afebrile after eight, twenty-four, seventy-two, and twenty hours respectively. Only one blood culture was obtained in the first two of these four children. In the third, the original culture was contaminated and the meningococcus was cultured from a blood sample drawn forty-eight hours after entry. The fourth patient had positive blood cultures obtained at the time of admission and on the following morning. The patients who were given sulfonamides usually responded very promptly to the customary doses of the drug, although the older patients as a rule required a somewhat longer time to become afebrile. Recovery was slow in the one patient with apparent chronic meningococcemia, with little real evidence of immediate benefit from the sulfonamide.

SEVERELY ILL PATIENTS

The two patients (Cases 15 and 16) with acute, fulminating meningococcemia each entered the hospital with an illness of twenty-four hours or less. They became ill with vomiting, fever, and prostration, developed widespread petechiae and purpuric lesions, and at the time of admission were in a state of shock. One of these patients showed a leucocytosis of 25,000; the other had a white cell count of only 10,600 on admission, but as he rallied from his shock the leucocytes numbered 38,150, with 76 per cent polymorphonuclears. Both of these patients had blood cultures positive for the meningococci, one belonging to Group I and the other being untypable. Both had normal spinal fluid findings with sterile cultures. Both patients were treated with massive doses of penicillin and sulfonamides in addition to the administration of parenteral fluids. One patient, who recovered after five days of fever, also received adrenal cortical extract. This was not available for the other patient, who died four hours after admission. The autopsy on the patient who died showed general visceral congestion but no adrenal hemorrhage.

COMMENT

One of the most significant features of this group of patients is that meningitis was not induced by lumbar puncture even when it was performed within a few minutes to an hour of the time when bacteremia was demonstrated by withdrawing blood samples containing meningococci from the patients. This sequence occurred in ten patients, including the fourth untreated patient described above, and one patient with fulminating meningococcemia. In an eleventh patient who was untreated, a spinal tap was negative at the time of admission when the fever and rash were maximal. Blood which was drawn for culture at the same time became contaminated. In six of the ten patients who received sulfonamides, in whom lumbar punctures were done at the time positive blood cultures were taken, the absence of even minimal meningeal inflammation was confirmed by repeat punctures done not later than forty-eight hours after admission, and on two patients by punctures done at both twenty-four and

forty-eight hours. In two of these patients sulfonamides were first administered twenty-four hours after the initial lumbar puncture. In our patients with meningitis[14] there was not one who failed to show either meningeal inflammation or a positive spinal fluid culture for meningococci at the first examination. Thus, we have no patient in whom there is evidence that meningitis was induced by a lumbar puncture during a period of bacteremia. This observation is of considerable importance as it tends to confirm the work of Pray,[20] who, working with pneumococci, showed that while it is theoretically possible to infect the meninges in this manner, the likelihood of such an occurrence is extremely remote. Similar results in patients with meningococcemia have been reported by Potter and associates.[10]

The patients in this group are typical of the cases of meningococcemia seen in civilian practice rather than in an army camp. The greatest incidence of the disease is in infants and children. In the majority of cases the disease is mild, at times even evanescent, though the occurrence of meningitis after weeks or even months of illness was a common experience before the use of sulfonamides in treatment.[8] In patients with a mild infection, the diagnosis is very difficult. It usually is suggested by the presence of a skin rash, though this is not always so. The diagnosis can be confirmed most readily by taking blood for culture. This should be done on all patients with a suggestive rash, as well as on all patients with an unexplained fever. By this means only can the diagnosis be established early when the condition is relatively mild. Delay enhances the probability of meningitis which, even in patients with a mild meningococcemia, may be extremely severe.

Severe, fulminating meningococcemia fortunately is rare. Among 296 patients with meningococcic infections, we have encountered only four instances. Meningitis was associated in two of these patients. Three of them have died, all within six hours after admission.

The immune response in patients with meningococcemia is quite similar to that in patients with meningitis. By using the technique of blood serum agglutinations,[18] we have found, in the patients studied, curves of agglutination titers to be quite comparable. In the absence of a positive blood culture, the diagnosis can be established by this procedure (Case 9).

SUMMARY

1. Sixteen cases of acute meningococcemia occurring in a general hospital and involving age groups from 2 months to 54 years have been reported. The disease in fourteen patients was characterized by a mild course which cleared up readily with sulfonamide treatment and, in some instances, before sulfonamides were administered. Two patients had severe, fulminating infections which clinically resembled the Waterhouse-Friederichsen syndrome. One of these patients died.

2. Serum agglutinin titers against meningococci were studied in four patients and were found to be present in all of them. The maximum titers obtained were from 1:16 to 1:128.

3. Lumbar puncture during the course of meningococcemia did not result in the development of meningitis in any of the twelve patients on whom it was performed.

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THE COMPARATIVE EFFECT OF PARENTERAL ADMINISTRATION OF SINGLE MASSIVE DOSES OF VITAMIN D IN AN OIL-ETHER VEHICLE

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MASSIVE doses of vitamin D have been widely used since their first experimental and clinical trial in 1928.[1] The oral route of administration is the most common. Oily solutions of vitamin D have also been intramuscularly injected with satisfactory results. In 1940, one of the authors[2] advocated the parenteral administration of massive doses of vitamin D in an oil-ether vehicle in order to enhance vitamin D absorption.

The speed of absorption of an intramuscularly injected drug depends chiefly on the extent of surface contact between its solvent and the tissues, and the solubility of the drug in the tissues. In the case of an oily solution of vitamin D, both factors are favored by the addition of ether to the oily solvent. Ether materially decreases the viscosity of oil. The alteration of the viscosity follows a hyperbolic curve, i.e., a relatively small proportion of ether reduces the viscosity of oil to a fraction of its original viscosity. As a result, this oil-ether vehicle forms a larger contact surface with the muscle interstices than oil alone, which has been experimentally demonstrated.[2] Moreover, since vitamin D is more soluble in ether than in oil, the ether carries vitamin D to the cell sterols and fats, thus increasing the solubility of the vitamin in the tissues. In this way, vitamin D can be rapidly absorbed while the oil may remain in situ for months.

Clinical observations[2] indicates that the parenteral injection of 600,000 units of calciferol in an oil-ether vehicle cured rickets and tetany at least as promptly as the oral administration of an equal dose of vitamin D; it seemed to be superior to the parenteral injection of vitamin D in oil.

However, an exact evaluation of the comparative efficacy of these three modes of vitamin D administration is lacking. Clinical observations would only reveal differences of a greater magnitude than are to be expected. An exact, comparative evaluation calls for animal experiments with their well-controlled and equal conditions.

The present study attempted such an evaluation by therapeutic and prophylactic experiments on rats.* Rachitic albino rats and normal weanlings of the same species respectively were used. In both types of experiments the animals were maintained on the *United States Pharmacopoeia* rachitogenic diet No. 2. Both the diet, and distilled water from glass-tipped bottles, were available to the animals ad libitum. The test doses were administered only once,

*Carried out in the Food Research Laboratories (Dr. B. L. Oser).

and in such dilution that each rat received 1,000 U.S.P. units of pure crystalline vitamin D_2 (calciferol) in 0.1 c.c. of solution. Persic oil was used as solvent for the oral doses, and persic oil, and a mixture of 6 parts of persic oil and 4 parts of U.S.P. ether respectively as solvents for the parenteral administration of vitamin D.

THERAPEUTIC EXPERIMENTS

Litters of weanling albino rats weighing between 45 and 60 Gm. were distributed into groups of four and fed the rachitogenic diet throughout a depletion period of eighteen to twenty-five days' duration. At the end of the depletion period, roentgenograms were taken of the right knee joint of each animal, and the rats distributed into experimental groups. During the test period the animals were kept in individual, wire-mesh, raised-bottom cages. There were three main groups of thirty animals each, divided according to the method of vitamin D administration, and three subdivisions of each based on the duration of the observation period. Each subgroup consisted of ten rats, five males and five females. The first subgroup for each type of treatment was roentgenographed on the second day and killed on the third to permit estimation of the degree of recalcification by the line test. The second subgroup was roentgenographed on the third and fourth, and sacrificed on the fifth day following dosage. The third subgroup was x-rayed on the third, fourth, and fifth days, and killed on the sixth for line tests. The experimental plan is outlined in the following table:

TABLE I. OUTLINE OF EXPERIMENTAL PLAN OF STUDY ON RATS

GROUP	NO. RATS	1,000 UNITS VITAMIN D_2 DILUTED IN	ROUTE OF ADMINISTRATION	X-RAYED AFTER (DAYS)	TERMINATED FOR LINE TEST AFTER (DAYS)
A	10	Persic oil	Oral	2	3
B	10	Persic oil	Oral	3,4	5
C	10	Persic oil	Oral	3,4,5	6
D	10	Persic oil	Intramuscular	2	3
E	10	Persic oil	Intramuscular	3,4	5
F	10	Persic oil	Intramuscular	3,4,5	6
G	10	Persic oil	Intramuscular	2	3
H	10	and ether	Intramuscular	3,4	5
I	10	(6:4)	Intramuscular	3,4,5	6

The oral dose was administered directly into the stomach by means of a 1 c.c. tuberculin syringe equipped with a No. 18 needle having a ball-tip adaptor to facilitate insertion through the esophagus. The intramuscular dose was injected slowly into the muscles of the right hind leg.

At the beginning of the test period, the tibias of all animals were found to have wide rachitic metaphyses. The appearance of new deposits of calcium in the provisional zone of calcification, the so-called line of healing, was rated in the roentgenographs on an arbitrary scale of 0 to 4, indicating the increasing width of the line.

TABLE II. SUMMARY OF DATA FOR RACHITIC RATS ADMINISTERED A SINGLE DOSE OF 1,000 USP UNITS OF VITAMIN D_2

GROUP	METHOD OF DOSAGE	AVERAGE BODY WEIGHT (GM.)			AVERAGE DEGREES OF HEALING AS ESTIMATED BY					
		DEPLETION PERIOD		ASSAY PERIOD	ROENTGENOGRAPH			LINE TEST		
		INITIAL	FINAL	FINAL	2 DAYS	4 DAYS	5 DAYS	3 DAYS	5 DAYS	6 DAYS
A	Oral in oil	49.3	68.5	70.3	0.05			2.04		
B	Oral in oil	53.3	70.3	74.5	0.75	2.55			2.94	
C	Oral in oil	51.2	72.0	76.9	0.35	1.9	2.63			3.13
D	Intramuscular in oil	48.5[8]*	67.0[8]	68.1[8]	0.19[8]			2.04[8]		
E	Intramuscular in oil	50.7[9]	72.4[9]	76.0[9]	0.39[9]	1.50[9]			2.62[9]	
F	Intramuscular in oil	50.6	69.7	74.6	0.33	0.98	1.75			2.57
G	Intramuscular in oil-ether	50.8	75.4	78.1	0.15			2.01		
H	Intramuscular in oil-ether	49.8	72.2	75.9	0.15	2.15			2.79	
I	Intramuscular in oil-ether	51.0[9]	69.6[9]	74.1[9]	0.67[9]	2.37[9]	3.09[9]			3.32[9]

*Superscripts represent number of animals per group; where not indicated, groups consist of ten animals each.

When each of the subgroups was terminated, the tibias were examined by the line test. The degree of healing was rated in accordance with the scale of Bills, Honeywell, Wirick, and Nussmeier.[3]

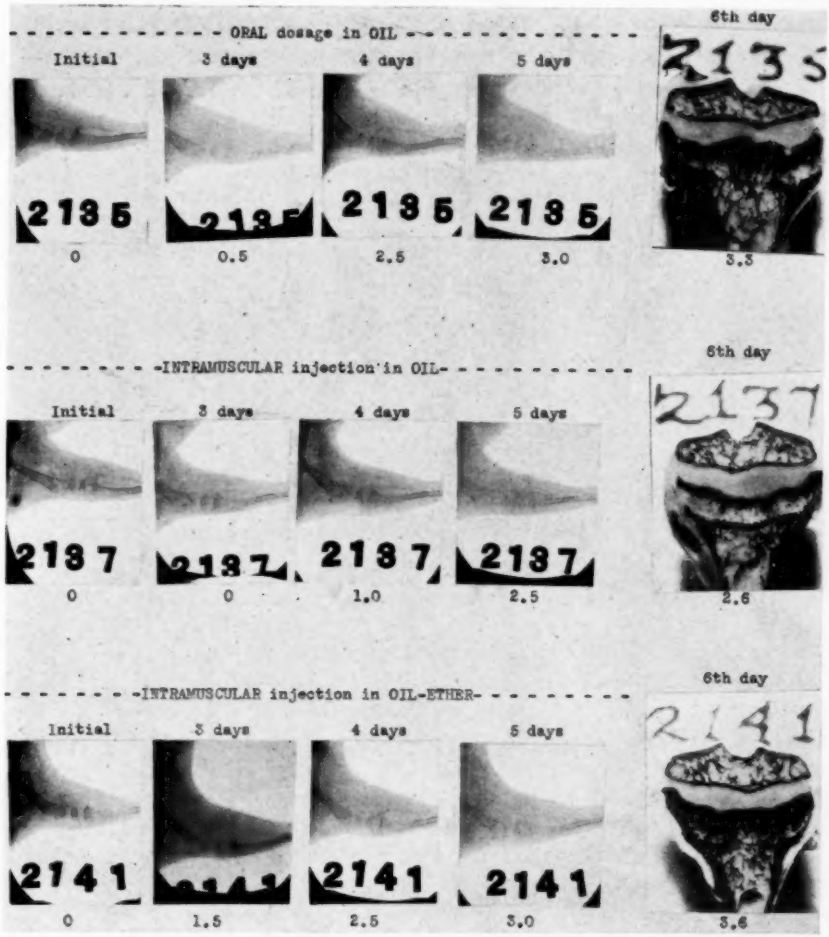

Fig. 1.—Photographs representative of the three treatment groups, showing progress of recalcification of rachitic tibias over a six-day observation period.
Figures below roentgenographs represent degrees of healing (scale 0 to 4).
Figures below microphotographs represent line test ratings (Bills' scale).

Table II contains the results of the therapeutic experiments. Two animals in Group D, and one each in Groups E and I failed to respond to the vitamin D dosage at all, and were omitted from the calculations. A representative series of roentgenograms and magnified microphotographs of tibias of the three groups appears in Fig. 1.

While the roentgenograms are of value in following the course of recalcification in individual animals, the enlarged microphotographs of the tibias show more clearly the difference in the effects of the three methods of vitamin D administration. The evaluations have therefore been based on the line test data. These have been subjected to statistical analysis, and the average responses, their standard errors, and the significance of the differences between the averages appear in Table III. For the size of the groups used in these experiments a t-value of 2.1 or more indicates significance in the differences between any two averages.

TABLE III. SUMMARY OF STATISTICAL DATA FOR THERAPEUTIC TESTS

GROUP	METHOD OF DOSAGE*	DURATION OF TEST (DAYS)	DEGREES OF HEALING† (LINE TEST RATINGS)		SIGNIFICANCE OF DIFFERENCE‡	
			AVERAGE	STANDARD ERROR	GROUPS COMPARED	T-VALUE
A	OO	3	2.04	±0.067	A and D	0
D	IMO	3	2.04^{8}	±0.080	D and G	0.3
G	IMOE	3	2.01	±0.122	G and A	0.3
B	OO	5	2.94	±0.176	B and E	1.2
E	IMO	5	2.62^{9}	±0.205	E and H	1.0
H	IMOE	5	2.79	±0.159	H and B	0.5
C	OO	6	3.13	±0.128	C and F	3.4
F	IMO	6	2.57	±0.109	F and I	4.0
I	IMOE	6	3.32^{9}	±0.122	I and C	1.1

*OO, Oral, in oil medium; IMO, intramuscular in oil medium; IMOE, intramuscular in oil-ether medium.

†Superscripts indicate the number of observations used in calculating the averages. Those omitted were completely negative responses.

‡For groups of this size, a t-value of 2.1 indicates a significant difference.

Table III shows that differences in the effect of the three methods of treatment are not significant three and five days after the administration of vitamin D. However, by the sixth day, when recalcification is well advanced, the superiority of the intramuscular injection of vitamin D in oil-ether solution as well as of the oral administration of vitamin D in oil over the intramuscular administration in oil is statistically significant, as indicated by t-values of 3.4 and 4.0 respectively. The intramuscular injection of vitamin D in oil-ether was somewhat more effective than the oral administration of vitamin D in oil.

PROPHYLACTIC EXPERIMENTS

The experimental conditions were similar to those of the therapeutic experiments. However, the prophylactic doses of vitamin D were administered immediately after weaning, when the feeding of the rachitogenic diet was started. The observation period was three months.

A single dose of 1,000 units of calciferol was given to each animal by the routes described in the therapeutic experiments. Three groups of thirty animals each received the prophylactic doses orally in oil, intramuscularly in oil, and intramuscularly in oil-ether respectively. Each of these groups was divided

into three subgroups of ten rats which were killed for histologic examination of the bones after thirty, sixty, and ninety days respectively. After each of these intervals, all survivors were x-rayed to see whether any decalcification had taken place.

A summary of the observations appears in Table IV. Representative series of photographs demonstrating the progressive condition of a typical animal receiving each form of prophylaxis are shown in Fig. 2. The interpretation of the roentgenographs is based on a rating of the width of the metaphyses, using an arbitrary scale of 0 to 4 to indicate increasing degrees of decalcifica-

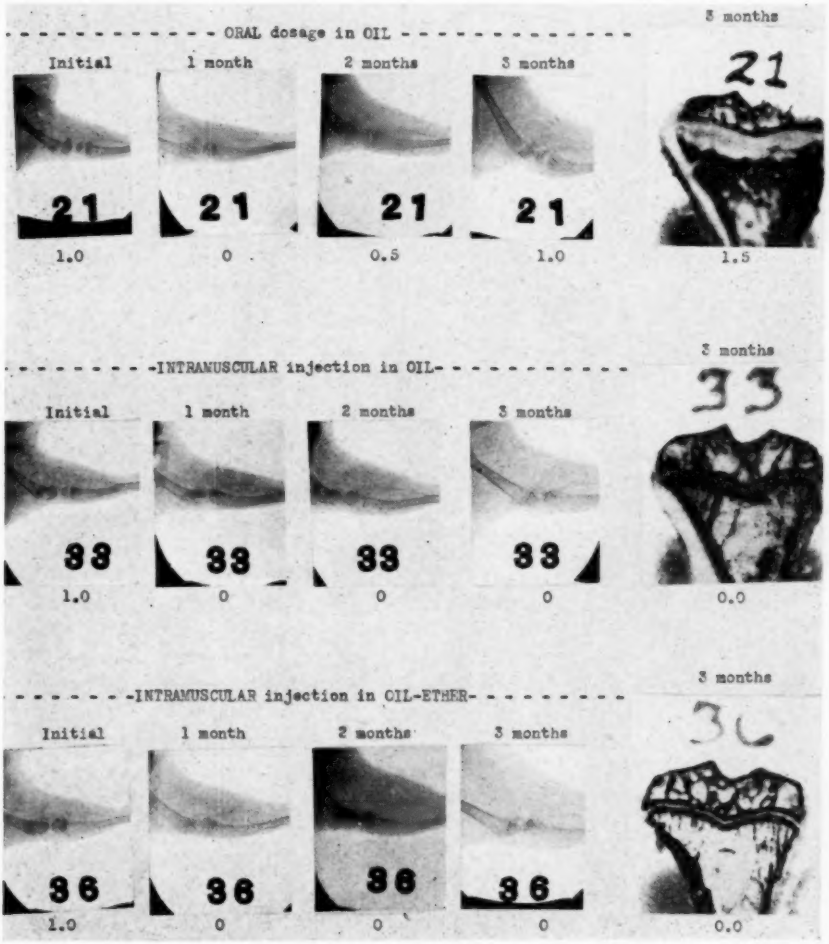

Fig. 2.—Photographs representative of the three treatment groups, showing development of metaphysis over a three-month period.

Figures below roentgenographs and microphotographs represent ratings for metaphysis widths (scale 0 to 4).

TABLE IV. SUMMARY OF DATA FOR RATS ADMINISTERED A SINGLE PROPHYLACTIC DOSE OF VITAMIN D_2

GROUP	METHOD OF DOSAGE	AVERAGE BODY WEIGHTS (GM.)				AVERAGE WIDTH OF METAPHYSIS AS ESTIMATED BY						
						ROENTGENOGRAPH				HISTOLOGIC TEST		
		0 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS	0 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS	1 MONTHS	2 MONTHS	3 MONTHS
J	Oil, oral	48.0	75.8			0.55	0.51			0.60		
K	Oil, oral	48.1[9]*	78.2[9]	121.9[9]		1.13[9]	0.28[9]	0.94[9]			0.85[9]	
L	Oil, oral	47.9	74.9	116.2	151.3	1.0	0.22	0.50	0.70			0.72
M	Oil, intramuscular	47.4	73.2			1.05	0.11			0.40		
N	Oil, intramuscular	47.4	80.3	120.1		1.09	0.23	0.13			0.07	
O	Oil, intramuscular	47.8	80.6	123.5	157.0	1.08	0.17	0.06	0.02			0.10
P	Oil-ether, intramuscular	47.8	79.4			0.95	0.48			0.56		
Q	Oil-ether, intramuscular	48.6	84.5	129.5		0.83	0.29	0.17			0.02	
R	Oil-ether, intramuscular	47.9	74.2	116.5	153.0	1.18	0.30	0.09	0.01			0.0

*Superscripts indicate number of animals per group. One rat in this group died and was omitted from the calculations.